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Evidence-based Series 2-23 Version 2- EDUCATION AND INFORMATION 2015

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 October 2015 put Evidence-based Series (EBS) 2-23 Version 2 in the Education and Information Section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. 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. Ed & Info 2015 Oct]. Program in Evidence-based Care Evidence-based Series No.: 2-23 Version 2 Education and Information 2015

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

Chemotherapy or Radiotherapy for Resectable Pancreatic Adenocarcinoma: Systematic Review

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: November 21, 2007

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.

INTRODUCTION

Pancreatic cancer is the fifth leading cause of cancer death in North America, with a five-year survival rate of 0.4 to 4% (1,2). Approximately 20% of patients presenting with pancreatic cancer have potentially surgically resectable disease. Of those undergoing laparotomy for an intended pancreatic resection, only 16-30% go on to have a resection. Therefore, only a small fraction of patients with pancreatic cancer will have a gross total resection of their tumour. Unfortunately, even in this highly selected subset of patients, the risk of recurrence and mortality remains unacceptably high, with a two-year overall survival of 18% to 36% in larger studies. The rationale for a practice guideline targeted to this specific subset of patients with pancreatic cancer is that a cure is possible and adjuvant treatment may benefit survival for these patients.

For the past 30 years, the treatment of patients after a pancreatic resection has varied from centre to centre, based on the interpretation of the results of a small randomized trial published by the Gastrointestinal Tumour Study Group (GITSG) (3,4). Some clinicians have accepted this trial as evidence of a survival benefit with postoperative chemoradiotherapy (CRT). A trial by the European Organization for Research and Treatment of Cancer (EORTC) (5) with a larger sample size reported no significant benefit for patients with pancreatic cancer receiving CRT,

but that trial was insufficiently powered to detect a survival difference between treatment groups. However, a recently published large multicentre trial by the European Study Group for Pancreatic Cancer (ESPAC) (6,7,8) has cast doubt on the conclusion of the GITSG study (3,4), stimulating a review of the available data.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle[1]. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Gastrointestinal Cancer DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the use of preoperative or postoperative chemotherapy and/or radiation in patients with resectable pancreatic cancer. The body of evidence in this review is primarily comprised of mature randomized controlled trial data; therefore, recommendations are offered. That evidence forms the basis of a clinical practice guideline developed by the Gastrointestinal Cancer DSG. The systematic review and recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is 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.

Literature Search Strategy

Entries to MEDLINE (1976 to November week 1, 2007), CANCERLIT (1983 to October 2002), and the Cochrane Library (Issue 4, 2007) were searched. "Pancreatic neoplasms" (Medical subject heading [MeSH]) was combined with the phrases "adjuvant" or "neoadjuvant" used as text words. Those terms were then combined with search terms for the following study designs or publication types: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials (RCTs) and clinical trials. A search of the 1999 through 2007 conference proceedings of the American Society of Clinical Oncology (ASCO) was also conducted. Reference lists of retrieved papers were scanned for additional citations.

Inclusion Criteria

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

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

Published abstracts or presentations of RCTs, including publicly available data from the ASCO Web site, were also considered.

Exclusion Criteria

The following were not included in this systematic review:

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

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.

Synthesizing the Evidence

Where possible, the data were pooled to estimate the overall effect on survival for the following comparisons: CRT versus no CRT and CT versus no CT. Pooling of survival data was performed at two years because these data were reported in all RCTs and two-year survival is considered a clinically relevant endpoint for patients with resectable pancreatic cancer. When the actual number of events (deaths) was reported, the reported data were used in the pooled analyses. The study results were pooled using Review Manager 4.2.7 (RevMan Analyses 1.0.2; version date: November 2003; © 2003 the Cochrane Collaboration)[2], which is freely available through the Cochrane Collaboration. Results are expressed as relative risk ratios (RR), where RR <1.0 favours the experimental treatment, RR >1.0 favours control, and RR=1 indicates no difference in risk between groups. The random effects model was used for meta-analysis as it provides the more conservative estimate of effect (9). Data on toxicity for the adjuvant treatment in the phase III trials were summarized but not pooled.

RESULTS

Literature Search Results

Preoperative Neoadjuvant Trials

One trial of preoperative CT and RT in patients with resectable pancreatic cancer was identified (10). This study has only been reported in abstract form, and few methodological details are available to assess study quality.

Postoperative Adjuvant Trials

Seven phase III RCTs of postoperative CT and/or RT versus surgery alone in patients with resectable pancreatic adenocarcinoma were identified (3-8,11-14). Details of specific CT and RT regimens are reported in Table 1. A review (15) of five of these trials (3,5,6,11,12) has been published, including a pooled analysis of individual patient data (IPD) from four trials (5,6,11,12). An additional meta-analysis was excluded because it included data from a non-randomized trial in its analysis (16). One RCT was a combination of three subtrials and was reported in several published papers (6-8). The final results from two of these subtrials were published as part of the IPD meta-analysis (15). The long-term follow-up results of one RCT, published separately, were included (17).

Study Quality

The randomization method was adequately described in five trials (3,6,11,13,14) and was not reported in three other trials (5,10,12). Patient stratification by prognostic factors was reported in all studies except the preoperative CRT study reported only in abstract form (10). None of the studies reported that patients or evaluators were blinded to treatment. Calculations to determine sample size and statistical power to detect a difference between treatment groups were reported in seven trials (3,5,6,11-14). One trial (3) was terminated early due to lower than anticipated accrual rates and an apparent survival difference between treatment arms. Five trials reported an intention-to treat analysis of all eligible randomized patients in the groups to which they were randomized (5,6,11,13,14). One trial excluded five out of 49 patients after randomization but before initiation of treatment, because of ineligibility or withdrawal of consent (3). One trial used a per protocol analysis and excluded 15 out of 173 patients with pancreatic cancer after randomization, because of ineligibility, withdrawal of consent, or protocol violation (12).

[2] RevMan Analyses [Computer program]. Version 1.0.2 for Windows. In: Review manager (RevMan) 4.2.7. Oxford (England): The Cochrane Collaboration, 2003.

Table 1. Randomized trials of preoperative or postoperative chemotherapy or chemoradiotherapy versus observation alone with curative pancreaticoduodenectomy.

Trial	Study Period (Years)	Chemotherapy or Chemoradiotherapy Regimen
GITSG/ Kalser (3,4)	1974-1982	Observation Split-course radiotherapy 2000 cGy x2 with 2 week break in 200cGy fractions with 5FU 500mg/m^2 iv days 1-3 and days 29-31 followed by 5FU 500mg/m^2 iv weekly for 2 years
EORTC/ Klinkenbijl (5,17)	1987-1995	Observation Split-course radiotherapy 2000 cGy x2 with 2 week break in 200cGy fractions with 5FU 25mg/kg/day civ days 1-3 and days 29-31
ESPAC1-2x2 Neoptolemos (6,7,8) *	1994-2000	Observation Split-course radiotherapy 2000 cGy x2 with 2 week break in 200cGy fractions with 5FU 500mg/m^2 iv days 1-3 and days 29-31 5FU 425mg/m^2 + LV20mg/m2 iv days 1-5 every 4 weeks x6 Chemoradiotherapy, then 6 months 5FU/LV
ESPAC1-plus Schema A (6,8,15)		Observation Split-course radiotherapy 2000 cGy x2 with 2 week break in 200cGy fractions with 5FU 500mg/m^2 iv days 1-3 and days 29-31
ESPAC1-plus Schema B (6,8,15)		Observation 5FU 425mg/m^2 + LV20mg/m^2 iv days 1-5 every 4 weeks x6
Norwegian/ Bakkevold (11)	1984-1987	Observation 5FU 500mg/m^2, doxorubicin 40mg/m^2, and MMC 6mg/m^2 iv every 3 weeks x6
Japanese/ Takada (12)	1986-1992	Observation MMC 6mg/m^2 iv, 5FU 320mg/m^2 iv days 1-5 plus 22-26 then oral 5FU 100mg/m^2 from week 5 “until progression”
Japanese/ Kosuge (14)	1992-2000	Observation Cisplatin 80mg/m2 day 1 + 5FU 500mg/m2 continuous infusion days 1-5, cycle repeated 4-8 weeks after start of first course
AIO/German Oettle (13)	1998-2004	Observation Gemcitabine 1000mg/m^2 iv day 1,8,15 every 4 weeks x6
Japanese/ Nakamori (10)	2001-2004	Observation Preoperative gemcitabine 400mg/m2 or 800mg/m2 on day 1 and 7 and concomitant accelerated hyperfractionated radiotherapy 1.5Gy x2/day, 5 days/week, total dose 30Gy or 36Gy.

Notes: 5FU, 5-fluorouracil; MMC, mitomycin-C; civ, continuous intravenous; d, day; LV, leucovorin; iv, intravenous; EORTC, European Organisation for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; GITSG, Gastrointestinal Tumour Study Group; AIO, Association of Medical Oncology of the German Cancer Society.
* See Appendix 1 for a schematic diagram of the ESPAC1 trial design.

Outcomes

Preoperative CRT Trial

One RCT of 38 patients published in abstract form compared preoperative CRT with gemcitabine and accelerated hyperfractionated RT to surgery alone for patients with resectable pancreatic cancer (10). No significant survival benefit was detected for patients who received preoperative CRT, although the study was likely underpowered to detect a significant difference between treatment groups (See Table 2). Adverse effects and quality of life data were not reported.

Table 2. Results of randomized adjuvant chemotherapy and chemoradiotherapy trials.

Trial	Treatment Group	# of Pts	Positive resection margins (%)	1 year overall survival (%)	2 year overall survival (%)	5 year overall survival (%)	Median Survival (months)
Japanese/ Nakamori (10)	Observation	19	21	70.6†	NR*	NR	16.7
	Preoperative CRT (Gemcitabine)	19	30	81.2†			17.6

Notes: CRT, chemoradiotherapy; Pts, patients; NR, not reported.
* 3-year overall survival: 15.4% in the observation group and 27.1% in the preoperative CRT group for patients who had R0 resection.
† Data reported for patients who had R0 resection.

Postoperative CRT Trials

Four RCTs compared postoperative CRT to observation or treatment without CRT (GITSG, EORTC, ESPAC1-2x2, and ESPAC1-plus Schema A) (3-8,15). One RCT of 43 patients by the GITSG (3,4) reported a significant survival benefit in patients who received split-course RT with 5FU, followed by maintenance 5FU once weekly for two years or until recurrence was noted compared to observation (see Table 3 for trial results). Comparison of the Kaplan-Meier survival curves demonstrated a significant survival benefit for patients receiving postoperative CRT over the follow-up period (unadjusted one-sided log rank p=0.035). The difference between the curves was greatest at two years post-surgery; however, few patients contributed to the survival estimate at that time point, and statistical power was not sufficient to detect a significant difference. There are uncertainties regarding the conclusions of the GITSG trial and their generalizability, because of the small number of patients and the exclusion of patients with positive resection margins. It is unclear from the results of that study whether the combination of CRT and additional postoperative CT was responsible for the observed survival benefit of treatment or whether that benefit was due to the prolonged administration of postoperative CT.

The EORTC trial (5) randomized 114 patients with pancreatic head adenocarcinoma to observation or combined CRT after resection. In contrast to the GITSG trial, the EORTC trial allowed the inclusion of patients with positive resection margins. Chemoradiotherapy was delivered in the same manner as in the GITSG study; however, no further CT was given after completion of RT. Comparison of the Kaplan-Meier survival curves did not demonstrate a significant survival difference between groups (two-sided log-rank p=0.099). While no statistically significant survival advantage was observed for patients receiving CRT, 17% of patients with pancreatic cancer in the treatment arm received no treatment due to patient refusal or treatment complications. The long-term results of this study after a median follow-up of 11.7 years were published in 2007 (17). No significant difference in survival was observed for patients with pancreatic head cancer in this analysis, with a mortality hazard ratio (HR) of 0.76 (95% confidence interval [CI] 0.52 to 1.12; log-rank p=0.165). It must be noted that the EORTC trial was statistically underpowered to detect a survival difference between treatment arms in patients with pancreatic cancer.

Two subtrials of the ESPAC-1 RCT reported no benefit in survival for patients receiving CRT compared to control. The ESPAC-1 trial (6,7,8) could be most accurately described as a combination of three subtrials with varying randomization schemes. (See Appendix 1 for a schematic diagram of the ESPAC-1 trial design.) A total of 541 eligible patients with pancreatic ductal adenocarcinoma were randomized after resection into one of three designs by clinician preference. Patients with positive resection margins were included in the study. In the 2x2 factorial design, 285 patients were randomized to observation, CT, CRT, or CRT followed by CT. That subtrial was designed to detect a difference between the overall comparisons of CRT versus no CRT and CT versus no CT and was not statistically powered to detect a difference between individual randomized groups. Results for individual groups and overall comparisons are reported in Table 3. The 2x2 subtrial reported a two-month increase in median survival for patients who did not receive CRT, but that difference was not statistically significant (p>0.05). Two-year overall survival was 40% in patients who did not receive CRT compared to 30% in patients who received CRT (p>0.05) (7). A second subtrial (ESPAC-1-plus A) randomized 68 patients to either observation or CRT, where additional postoperative CT was at investigator discretion (15). An 8% increase in overall risk of death was reported for patients who received CRT. A third subtrial (ESPAC-1-plus B) randomised 188 patients to either observation or CT, where postoperative RT was at investigator discretion (15). That subtrial is discussed in the postoperative CT section of this review. Patients in each subtrial were stratified according to additional background therapy and analyzed using an intention-to-treat analysis. Protocol violations were reported in 51 out of 541 patients (9%) in a preliminary analysis: 25 patients refused to accept their assigned treatment, and 25 patients withdrew from their assigned treatment after initiation of therapy (6).

Table 3. Results of randomized postoperative chemotherapy and chemoradiotherapy trials.

Trial	Treatment Group	# of Pts	Positive resection margins (%)	1 year overall survival (%)	2 year overall survival (%)	5 year overall survival (%)	Median Survival (months)
GITSG/ Kalser (4)	Observation	22	0	50	18	NR	10.9
	CRT→5FU 2years	21	0	67	43	NR	21.0
EORTC/ Klinkenbijl (5,17) ¶	Observation	54	25‖	52†	23	10	12.6
	CRT	60	20‖	70†	37	20	17.1
ESPAC1-2x2 Neoptolemos (6-8) §	Results for randomized groups						
	Observation	69	NR	NR	NR	11	16.9
	CRT	73				7	13.9
	5FU/LV	75				29	21.6
	CRT → 5FU/LV	72				13	19.9
	Results for overall comparisons						
	No CRT (Obs and 5FU/LV)	144	16	NR	41	20	17.9
	CRT (CRT and CRT→ 5FU/LV)	145	19		29	10	15.9
	No CT (Obs. and CRT)	142	16	NR	30	8*	15.5*
	CT (5FU/LV and CRT→5FU/LV)	147	19		40	21*	20.1*

Trial	Treatment Group	# of Pts	Positive resection margins (%)	1 year overall survival (%)	2 year overall survival (%)	5 year overall survival (%)	Median Survival (months)
ESPAC1-plus Schema A (15)	No CRT	36	NR	NR	23.5	NR	13.0
	CRT	33			24.6		12.5
ESPAC1-plus Schema B (15)	No CT	95	NR	NR	26.8*	NR	12.7*
	CT (5FU/LV)	97			48.9*		24.0*
Norwegian/ Bakkevold (11)	Observation	31‡	0	45	32	8	11*
	DOX/MMC/5FU	30‡	0	70	43	4	23*
Japanese/ Takada (12)**	Observation	77	83	53†	30†	18	12†
	MMC/5FU	81		53†	25†	11.5	12†
AIO/German Oettle (13)	Observation	175	15	72	42	11.5	20.2
	Gemcitabine	179	19	72	48	22.5	22.1
Japanese/ Kosuge (14)	Observation	44	0	NR	NR	14.9	15.8
	5FU/cisplatin	45	0			26.4	12.5

Notes: 5FU, 5-fluorouracil; CRT, chemoradiotherapy; CT, chemotherapy; DOX, doxorubicin; LV, leucovorin; MMC, mitomycin-C; NR, not reported; Pts, patients; EORTC, European Organisation for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; GITSG, Gastrointestinal Tumour Study Group; AIO, Association of Medical Oncology of the German Cancer Society.

* Difference is statistically significant (p<0.05).

† Estimated from survival curves.

‡14 of 61 patients had carcinoma of the ampulla of Vater.

§ See Appendix 1 for a schematic diagram of the ESPAC1 trial design.

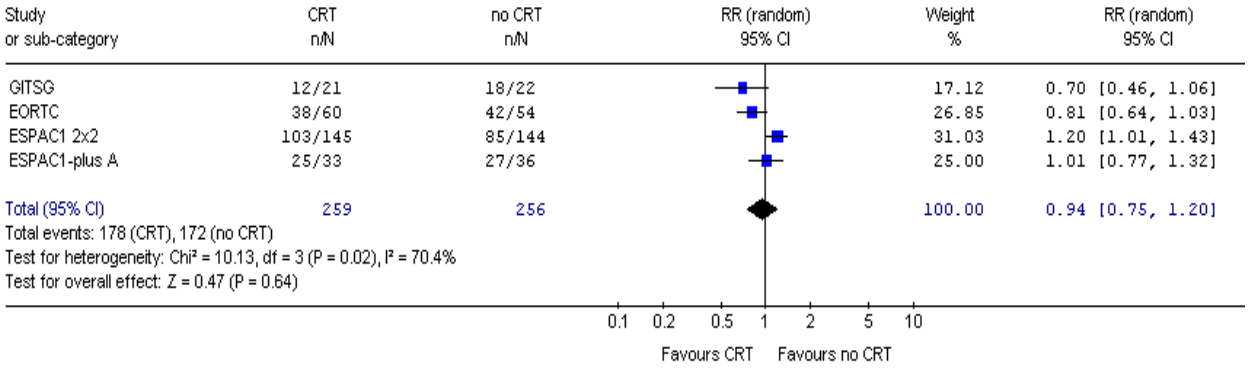
II Resection margin percentages are for all patients, including periampullary cancer (Observation n=103, CRT n=104)

¶ Results are for pancreatic head cancer subgroup. Long-term follow-up data (17): median survival 1 year versus 1.3 years favouring the treatment arm.

** Results are for pancreatic cancer subgroup.

Results of the four trials reporting data on patients randomized to observation versus an arm containing postoperative concurrent CRT were pooled. The meta-analysis indicated no difference in two-year mortality, with a risk ratio of 0.94 (95% confidence interval [CI]; 0.75 to 1.20, p=0.64). Significant heterogeneity was detected between studies (p=0.02) (Figure 1).

Figure 1. Risk ratio of two-year mortality with postoperative chemoradiotherapy.



Postoperative CT Trials

Six RCTs compared postoperative CT to observation or CRT (ESPAC1-2x2, ESPAC1-plus Schema B, Norwegian, Japanese/Takada, and the Association of Medical Oncology

[AIO]/German, Japanese/Kosuge) (6-8,11-15). All CT regimens were 5FU-based, except for the AIO/German trial (13) in which patients in the treatment arm received gemcitabine. See Table 1 for treatment regimens and Table 3 for trial results.

The results of all the RCTs except the Japanese trial by Takada et al (12) favoured the treatment arm receiving postoperative CT. The Norwegian phase III trial (11) of 61 patients with negative resection margins included 14 patients with carcinoma of the ampulla of Vater. Only 24 of the 30 patients randomized to the treatment arm received any CT, and only 13 patients completed all six cycles. Results were not stratified according to tumour location. A significant improvement in median survival (23 months versus [vs.] 11 months, p=0.02) and survival over two years based on analysis of Kaplan-Meier survival curves (generalized Wilcoxon p=0.04) was reported. However, long-term survival was not significantly different between treatment arms. Estimates of HRs for the ESPAC1-2x2 (7) and ESPAC1-plus B (15) trials demonstrated a significant improvement in survival for patients receiving postoperative CT. Reduction in overall risk of death was 29% and 46%, respectively, for patients in the treatment arm of each trial (15). Patients with positive resection margins comprised 18% of the ESPAC1-2x2 trial and 23% of the ESPAC1-plus trial. Survival advantage in the 2x2 randomization group appeared to be greater in patients without background CRT. A secondary analysis demonstrated a survival benefit for CT irrespective of method of surgical resection or postoperative complications (18).

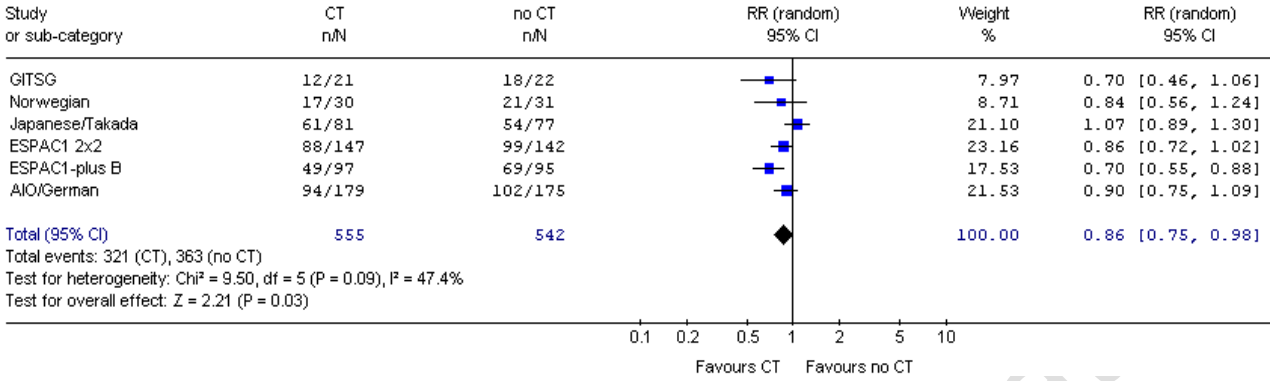
The German AIO CONKO-001 study randomised 368 patients to either observation alone or six months of gemcitabine (13). Disease-free survival, the primary endpoint of the study, was significantly increased in patients who received gemcitabine compared to patients in the control arm (median 13.4 months vs. 6.9 months; log-rank p<0.001). There was no significant improvement in overall survival in the intent-to-treat population for patients who received gemcitabine compared to patients who underwent surgery alone (log-rank p=0.061); however, the majority of patients in the observation arm received gemcitabine after relapse, and some patients received additional lines of chemotherapy. A pre-specified qualified analysis included only patients who received at least one complete cycle of gemcitabine in the treatment group and patients who received no postoperative therapy in the control group. In this analysis, survival was significantly improved in patients who received gemcitabine compared to patients in the control group (median 24.2 months vs. 20.5 months; log-rank p=0.02).

The Japanese study by Kosuge et al (14) randomised 89 patients to observation alone or postoperative CT with cisplatin and 5FU. Patients with positive resection margins were not included in the trial. Median survival and five-year survival were not significantly different between treatment groups (p=0.94).

The Japanese phase III study by Takada et al (12) included 173 patients with resected pancreatic cancer, but only 158 were included in the analysis. Patients were randomised to observation or perioperative plus postoperative CT. In that study, there was no significant difference seen with the addition of CT (p>0.05), although the trend was in favour of observation alone. Nine percent of patients were excluded after randomisation in that per-protocol analysis. A high proportion of patients in the trial had positive resection margins (83%).

Pooling of the results of patients randomized to an arm containing a prolonged period (>4 months) of postoperative CT versus without postoperative CT (3,6,11-13,15) demonstrates a significant reduction in two-year mortality, with a risk ratio of 0.85 (95% CI 0.75 to 0.98, p=0.03) (Figure 2). The GITSG trial (3,4) was included in the pooled analysis because patients in the treatment arm received maintenance 5FU for two years or until recurrence. The Japanese study by Kosuge et al (14) did not provide sufficient survival data at two years to be included in the pooled analysis. Moderate heterogeneity between studies was detected using a significance level of 0.1 (p=0.09). That was due to the inclusion of the Japanese trial by Takada et al (12) in which a higher proportion of patients had positive resection margins compared to the other trials included in the pooled results.

Figure 2. Risk ratio of 2 year mortality with postoperative chemotherapy



Published IPD Meta-analysis of Postoperative Trials

A single published meta-analysis of postoperative therapy trials was identified (15) that included five of the six randomized trials (GITSG, EORTC, Norwegian, Japanese, and ESPAC-1) (3,5,6,11,12). Individual patient data was available for 875 patients from four of those trials (EORTC, Norwegian, Japanese, and ESPAC-1). The pooled analysis indicated a 25% relative reduction in risk of death with CT compared to no CT (HR=0.75, 95% CI 0.64 to 0.90, p=0.001) with an improvement in median survival (19.0 vs. 13.5 months), two-year overall survival (38% vs. 28%) and five-year overall survival (19% vs. 12%). No benefit was demonstrated for the use of combined CRT (HR=1.09, 95% CI 0.89 to 1.32, p=0.43), with median survivals with CRT compared to no CRT being 15.8 and 15.2 months, respectively. Similarly, two-year overall survival was 30% versus 34% and five-year survival was 12% versus 17%, demonstrating no advantage for CRT. In subgroup analysis, there was heterogeneity of patients based on margin status, where the effect of therapy was dependent on margin status for both CRT (χ^2_1=4.2, p=0.04), and CT (χ^2_1=7.3, p=0.007). In the margin-positive patients, postoperative CT appeared less effective (overall survival 16.5% in CT group vs. 19.3% in no-CT group, p>0.05), and CRT appeared more effective (overall survival 22.6% in the CRT group vs. 15.1% in the no-CRT group, p>0.05). It must be noted that this subgroup analysis was an observational comparison, and there was insufficient statistical power to detect significant survival differences between treatment arms within subgroups.

Adverse Effects

Adverse effects reported in the phase III trials differed between treatment groups. In the GITSG trial (3), there were four adverse reactions in the treatment group. Three patients developed leukopenia with a white blood cell (WBC) count of 1.5 to 1.9 x106/L, and one patient developed a rash. No life-threatening toxic reactions or deaths due to therapy were reported.

In the EORTC study (5), 35 (44%), patients received only three days of 5FU CT during the second course of RT, because of grade one or two toxicity. No leukopenia or thrombocytopenia worse than World Health Organization (WHO) grade one occurred. A further seven patients developed minor toxicity, especially nausea and vomiting. In one patient, full treatment was not completed due to the development of duodenal ulceration, which precluded administration of the second course of RT.

The ESPAC study only collected toxicity data in a substudy involving centres with “resources to complete and return requested information,” in what appears to be a poorly controlled fashion (6). In those 246 patients, grade 3-4 toxicities were seen in 1 out of 74 patients on CRT, 28 of 118 on CT, and 25 of 54 on CRT and CT. The most common side effects were stomatitis (32%), neutropenia (25%), and diarrhea (10%). Dose reductions of 5FU occurred in 22% of patients.

In the Norwegian study (11), only 24 of the 30 patients randomized to postoperative treatment with 5FU, doxorubicin, and mitomycin-C (MMC) received any CT. Toxicity was generally excessive in treated patients. Of 22 patients evaluable for toxicity, 16 (73%) were hospitalised due to toxicity during the first course of CT. Only 13 patients were able to complete all six scheduled courses, and six of those patients were hospitalised during their last treatment course. Gastrointestinal toxicity, mainly grade one, was the most common adverse reaction. Hematological toxicity was noted as moderate. Cardiotoxicity and nephrotoxicity were each observed in two patients. Five patients developed sepsis during treatment, with one toxic death.

The German AIO study of postoperative gemcitabine versus observation reported that gemcitabine was well-tolerated and severe (grade 3 or 4) toxicity was rare (13). In the gemcitabine group, 26 out of 186 patients experienced serious adverse events, only five of which were considered treatment-related.

The Japanese study by Kosuge et al (14) comparing postoperative cisplatin and 5FU to surgery alone reported that minor toxicity (grade 1 or 2) was common, especially nausea and vomiting, and a few patients experienced toxicity of grade 3 or higher. All toxicities were resolved with conservative treatment.

Quality of Life

Patients in the ESPAC-1 trial completed quality of life questionnaires every three months (6). Data for three-month changes in quality of life were available for 211 out of 541 patients (39%) (6), representing an unselected subset of patients. No significant differences were observed in the mean overall quality of life score change within the first three months between the CRT group and the no CRT group or between the CT group and the no-CT group. Mean overall scores improved similarly for all treatment groups in this time period. Fifty-three percent of patients (152 out of 289) in the ESPAC-1 2x2 factorial trial provided quality of life data for the first 12 months following resection (7). No significant differences were observed in mean quality of life score within this period between the CRT group and the no-CRT group (p=0.17) or between the CT group and the no-CT group (p=0.75).

Three additional postoperative CT trials provided quality of life data (11-13). The Norwegian study (11) reported that patients in the treatment and control groups had similar clinical performance up to 12 months following resection. Karnofsky's performance score was 80 in the CT group and 90 in the observation group at three months following resection and 90 in both groups after this time point. The Japanese study by Takada et al (12) reported no significant difference in ECOG performance score or body weight between the CT group and the observation group. The German study of postoperative gemcitabine versus surgery alone (13) reported a similar increase in median Karnofsky performance status from 80% to 90% in both groups and no significant differences in quality of life between groups, as measured by the Spitzer questionnaire.

DISCUSSION

Clinical trials of postoperative therapy for patients with resectable pancreatic cancer to date have been constrained by methodological limitations that make decisive conclusions difficult to reach. The GITSG study (3) included few patients, and the EORTC study (5) did not stratify patients by resection margin status and lacked sufficient statistical power to detect a survival difference between groups for patients with pancreatic cancer. The ESPAC-1 trial (6) introduced considerable selection bias by allowing clinicians to choose the randomization scheme to which patients were entered; however, the authors published the results of the ESPAC 2x2 factorial design separately, which were free of data contamination and represented a clean methodological design (7). Patients in the ESPAC-1-plus trials were allowed to receive background therapy outside of the randomly assigned regimen, according to patient or physician preference, thus confounding the results of the comparisons. The ESPAC-1 trial

reported that a considerable number of patients did not receive treatment according to protocol and variations in radiotherapy quality control were allowed between study centres. Of the patients for whom treatment details were available, 21% who were randomized to receive CRT were given more or less than 40 Gy, and 9% received no CRT, while 33% who were randomized to receive CT were given less than six cycles, and 17% received no CT. Similarly, a significant number of patients randomized to the treatment arm of the Norwegian postoperative CT trial (11) were not treated (20%) or did not complete therapy (37%). The Japanese study by Takada et al (12) did not use an intention-to-treat analysis. Those limitations make the interpretation of some study results problematic and underline the importance of sufficiently powered trials with clean methodological designs to better clarify the role of postoperative therapy in this patient group.

The initial positive result of the small GITSG study (3,4) that led to a conventional recommendation for postoperative CRT has been refuted by the larger ESPAC-1 trial (6-8). It now appears more probable that the GITSG study was positive not because of the CRT but rather the subsequent two years of postoperative CT. Postoperative CRT with split-course RT can no longer be routinely recommended for patients after resection of pancreatic cancer. However, it is possible that CRT could still be beneficial if given with superior modern treatment planning techniques, with the elimination of split-course RT regimens and when given in combination with newer CT agents such as infusional 5FU or gemcitabine. Additionally, the role of postoperative CRT in margin-positive patients requires clarification, as only a small minority of patients in those studies were margin positive. The IPD meta-analysis (15) suggested improved outcomes with CRT in margin-positive patients compared to margin-negative patients; however, there was insufficient statistical power to make comparisons between those subgroups. These are topics of relevance for future trials.

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

At present, there is more evidence available for the overall survival advantages seen with postoperative 5FU/LV than for gemcitabine in the postoperative setting. Most CT regimens used in the reported trials were 5FU-based for a period of at least four months. Given the extensive experience with the Mayo regimen in the colorectal cancer postoperative setting, and the use of this regimen in the largest trial (ESPAC-1), that would seem a reasonable choice for postoperative therapy. Although in the metastatic setting gemcitabine has been compared to 5FU/LV and found to be associated with better quality of life, studies comparing those two regimens in the postoperative setting are ongoing. The RTOG 9704 study (19) evaluated the addition of gemcitabine to postoperative adjuvant 5FU CRT. All patients received 5FU CRT and either 5FU or gemcitabine before and after CRT. In this study, 42% of patients randomized to the 5FU CRT plus 5FU crossed over to receive gemcitabine. The addition of gemcitabine to 5FU CRT improved survival in patients with pancreatic head cancer but not in the analysis of all eligible patients. Emerging data from the ESPAC-3 trial will determine if six months of postoperative gemcitabine is equivalent or superior to 5FU/LV. The higher drug acquisition cost of gemcitabine and longer administration time should be considered prior to the widespread adoption of gemcitabine as standard postoperative therapy over the more studied 5FU/LV regimen. There are currently insufficient data to support the routine use of preoperative therapy for patients with potentially resectable pancreatic cancer.

The Norwegian study by Bakkevold et al (11) demonstrated superior outcomes with combination chemotherapy using 5FU, doxorubicin, and MMC compared to observation alone. Although that study provides further evidence for the role of chemotherapy as postoperative

treatment, it is not possible to determine the independent effect of the doxorubicin or the mitomycin from the trial, and there is an absence of supporting data for those agents. In addition, significant toxicity was observed in patients who received the combined chemotherapy regimen. Therefore, the routine use of doxorubicin or MMC in the postoperative setting cannot be recommended.

ADMINISTRATION, DOSING AND SCHEDULING

- 5-fluorouracil is supplied as a 50 mg/ml solution in 500 mg, 2.5 g, and 5 g vials. For bolus administration, the dose is given undiluted as a rapid intravenous push over roughly five minutes.
- Leucovorin calcium is supplied as a 10 mg/ml solution in 50 ml vials. For bolus administration, the dose is given undiluted as a rapid intravenous push over roughly five minutes.

ONGOING TRIALS

The National Cancer Institute's (NCI) database of clinical trials (http://www.cancer.gov/clinicaltrials) was searched on November 21, 2007 for reports of relevant ongoing trials (Table 4).

Table 4. Ongoing trials of preoperative or postoperative therapy for resectable pancreatic cancer.

Phase III Randomized Adjuvant Study of Gemcitabine Versus Fluorouracil and Leucovorin Calcium Versus Observation in Patients With Completely Resected Pancreatic Cancer	
Protocol ID:	RLUH-NCRI-ESPAC-3, EU-20043, NCT00058201, AGITG-ESPAC-3, CAN-CIC-PA2 **(Study completed and published, please see section 4 for details)**
Date last modified:	June 28, 2007
Type of trial:	Randomized, active control
Primary endpoint:	Survival at 2 years
Accrual:	Expected enrolment 660
Sponsorship:	Royal Liverpool University Hospital, NCIC, Australasian Gastro-Intestinal Trials Group
Status:	Open to accrual
Phase II/III Randomized Study of Gemcitabine Followed By Chemoradiotherapy With Gemcitabine Versus Gemcitabine Alone After Prior Curative Resection in Patients With Pancreatic Head Adenocarcinoma	
Protocol ID:	EORTC-40013, EORTC-22012, EU-20540, NCT00064207, FFCD-0304
Date last modified:	January 25, 2007
Type of trial:	Randomized, active control
Primary endpoints:	Overall survival, tolerability, feasibility
Accrual:	Expected enrolment 538
Sponsorship:	EORTC, Federation Francophone de Cancerologie Digestive
Status:	Closed to accrual

CONCLUSIONS

Patients should be referred to a medical oncologist to discuss postoperative CT after gross complete excision of a pancreatic adenocarcinoma. Acceptable regimens include six months of 5FU plus folinic acid or single-agent gemcitabine. The role of postoperative CRT is not clear and warrants further study. Postoperative CRT is not recommended when used with a split-course RT schedule for patients with negative margins. In margin positive patients, there may

be a role for postoperative CRT. There is insufficient evidence regarding the use of preoperative CT or RT or the use of intra-operative RT.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

The Gastrointestinal Cancer DSG would like to thank Dr. D Jonker, Dr. E Bouttell, and Ms. K Spithoff for taking the lead in drafting and revising this systematic review with meta-analyses.

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

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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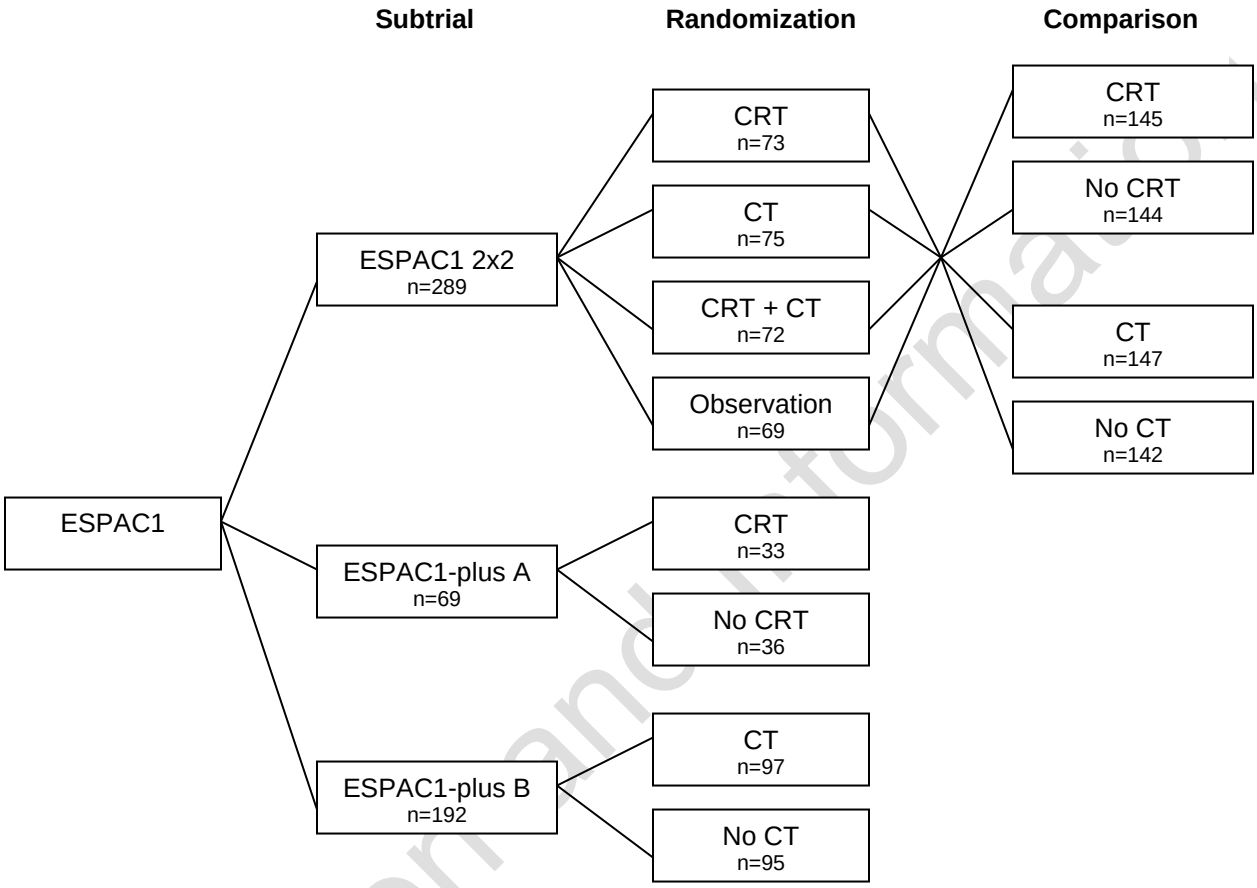
Appendix 1. European Study Group for Pancreatic Cancer 1 (ESPAC-1) multicentre randomized trial of adjuvant chemoradiotherapy (CRT) and chemotherapy (CT) in resected pancreatic cancer (6,7).



Ontario
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Evidence-based Series #2-23 version 2: Section 3

Chemotherapy or Radiotherapy for Resectable Pancreatic Adenocarcinoma: Guideline Development and External Review: Methods and Results

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)
Developed by the Gastrointestinal Cancer Disease Site Group

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.

Original Report Date: July 26, 2006
Current Report Date: November 21, 2007

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based clinical practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical

practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series:

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review—Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Gastrointestinal Cancer DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the use of preoperative or postoperative chemotherapy and/or radiation in patients with resectable pancreatic cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

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

- The first recommendation should be reworded to clearly indicate whether or not postoperative chemotherapy is recommended.
- Since most of the trials are included in the published meta-analysis, the group could use this as the evidentiary base and only discuss subsequent trials on an individual basis.
- Additional discussion of the quality characteristics and methodological limitations of some of the trials and how those limitations may affect the recommendations would be helpful.
- A diagram outlining the complex design of the ESPAC-1 trial would be helpful.

Modifications/Actions in Response to RAP Feedback

- The first recommendation was reworded to state that postoperative chemotherapy is recommended for patients with resectable pancreatic adenocarcinoma.
- The authors decided to retain a discussion of the individual trials to better outline the quality and limitations of the evidence for postoperative therapy included in the published meta-analysis.
- A section on study quality was added to the Results section of the Systematic Review. Further discussion on the limitations of several studies was added to the Discussion section of the Systematic Review.
- A diagram of the ESPAC-1 trial design was created and added to the Systematic Review as an appendix.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series and the review and approval of the report by the PEBC Report Approval Panel, the Gastrointestinal Cancer DSG

circulated the clinical Practice Guideline and Systematic Review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1: DRAFT RECOMMENDATIONS (approved for external review March 14, 2006)
Target Population These recommendations apply to adult patients with resectable pancreatic adenocarcinoma for whom a pancreatectomy is planned.
Recommendation • Postoperative adjuvant 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 (FU) 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 adjuvant radiotherapy. • There is insufficient evidence to support or refute the use of preoperative neoadjuvant chemotherapy or radiotherapy or the use of intra-operative radiotherapy.
Qualifying Statements • The efficacy of single-agent gemcitabine has only been reported in early results from one study published in abstract form and trials comparing 5-FU to gemcitabine are ongoing. The evidence is more convincing for 5-FU-based regimens; therefore, gemcitabine cannot currently be advocated over 5-FU. • Evidence of a possible role for radiotherapy in patients with margin-positive resections is limited to a subgroup analysis in which effect of therapy was dependent on margin status. Recommendations that there may be a role for adjuvant radiotherapy in suitable patients are based on 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 adjuvant radiotherapy when used with more modern treatment planning techniques.

Methods

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

Results

Twenty-nine responses were received out of the 59 surveys sent (49% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners

who responded, 19 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 5.

Table 5. Responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear.	19 (100)		
There is a need for a guideline on this topic.	18 (95)	1 (5)	
The literature search is relevant and complete.	19 (100)		
The results of the trials described in the report are interpreted according to my understanding of the data.	18 (95)	1 (5)	
The draft recommendations in the report are clear.	17 (89)	2 (11)	
I agree with the draft recommendations as stated.	17 (89)	2 (11)	
This report should be approved as a practice guideline.	16 (84)	3 (16)	
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	17 (89)	1 (5)	1 (5)

Summary of Written Comments

Four respondents (21%) provided written comments. The main points contained in the written comments were:

1. The value of the chemotherapy agents, 5FU or gemcitabine, was debatable and a practice guideline pancreatic cancer should state that most patients should be entered on trials, since "standard" therapy is not overwhelmingly effective.
2. This is a difficult topic since, despite the number of patients, there are so few trials. It is surprising that adjuvant 5-FU is effective. The comment on a possible role for adjuvant RT in margin-positive patients is warranted. The addition of a comment suggesting pre-operative treatment only in the setting of a trial should be considered.
3. The phrase "whipple" should not be used to reflect all resected cases since "whipple" is removal of the head of the pancreas. The guideline refers to all cases of pancreatic resection for adenocarcinoma.

Modifications/Actions

In response to feedback received from the practitioner feedback process, the following changes were made:

1. There is clinical importance to the improvement in survival, and therefore, the authors feel that chemotherapy should be offered. The DSG agrees that clinical trials in this population are important as there are a substantial majority of patients who are not cured even with chemotherapy. These clinical trials should include both adjuvant and neoadjuvant trials.
2. A Qualifying Statement was added to the Practice Guideline, suggesting that preoperative treatment should only be considered in the setting of a clinical trial.
3. The authors replaced all references to the phrase "whipple" with "pancreatic resection".

This report reflects the integration of feedback obtained from the Report Approval Panel of the PEBC and through the external review process, with final approval given by the Gastrointestinal Cancer DSG. This report was updated in November 2007 to incorporate new evidence. The following key changes were made:

- A Japanese trial of preoperative therapy for resectable pancreatic cancer reported in abstract form was identified and included; however, the results of this trial did not change the conclusion that there are insufficient data to support preoperative chemotherapy or radiotherapy (3).
- Long-term results of the EORTC trial and the full publication of the CONKO-001 trial were added to the Results section of the Systematic Review (4,5).
- A Japanese study comparing 5FU plus cisplatin to observation alone was added to the Results section of the Systematic Review (6).
- A discussion of the results of the RTOG 9704 trial comparing gemcitabine with 5FU that did not meet the inclusion criteria for this review was added to the Discussion section of the Systematic Review.

Further updates will be conducted as new evidence informing the question of interest emerges.

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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or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series #2-23 version 2: Section 4

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

Chemotherapy or Radiotherapy for Resectable Pancreatic Adenocarcinoma

Guideline Summary Review

D. Jonker, N. Ismaila, and the Gastrointestinal Cancer Disease Site Group

Review Date: April 2, 2013

The 2007 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2007.

In September 2011, 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 conducted an updated search of the literature. A clinical expert 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 1 (Clinical Practice Guideline) in April 2013.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Question Considered

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.

Literature Search and New Evidence
The new search from December 2007 to November 2012) yielded 14 references representing 6 meta-analysis, and 7 RCTs (1 RCT had 2 publications), evaluating the role of chemotherapy or radiotherapy for resectable pancreatic adenocarcinoma. Five of these references had full text publications and 9 were in abstract form. There was one ongoing study identified from clinicaltrials.gov. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations
The new data supports existing recommendations. Hence, the Gastrointestinal Cancer DSG ENDORSED the 2007 recommendations on the role of chemotherapy or radiotherapy for resectable pancreatic adenocarcinoma. However, a revision was made to the first qualifying statement and the wordings have been changed based on currently available evidence.

Document Review Tool

Number and title of document under review	2-23 Chemotherapy or Radiotherapy for Resectable Pancreatic Adenocarcinoma
Current Report Date	November 2007
Clinical Expert	Dr. Derek Jonker
Research Coordinator	Nofisat Ismaila
Date Assessed	September 2011
Approval Date and Review Outcome (once completed)	April 2, 2013 [ENDORSED]

Original Question(s):

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:

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

Study Section Criteria:

Inclusion Criteria

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

3. Published abstracts or presentations of RCTs, including publicly available data from the ASCO Web site, were also considered.

Exclusion Criteria

1. Letters and editorials.

2. Articles in a language other than English.

Search Details:

- December 2007 to November 2012 (Medline Aug wk 1 and Embase wk 32)
- January 2009 to January 2013 (ASCO Annual Meeting)
- December 2007 to January 2013 (clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:

Of 922 total hits from Medline, Embase + 37 total hits from ASCO + 68 total hits from clinicaltrials.gov, 14 references representing 6 meta-analysis, and 7 RCTs (1 RCT had 2 publications), were found evaluating the role of chemotherapy or radiotherapy for resectable pancreatic adenocarcinoma. Five of these references had full text publications and 9 were in abstract form. There was one ongoing studies identified from clinicaltrials.gov.

Meta-analysis					
Interventions	**Population**	**N of studies**	**Outcomes**	**Brief results**	**References**
Adjuvant chemotherapy/ chemoradiotherapy Vs. Surgery alone	Patients who had undergone a potentially curative resection and who had not received previous chemotherapy (N=1166)	8 RCTs	OS and DFS	• Adding adjuvant chemotherapy to patients with resectable PAC was associated with significantly increased median OS (odds ratio [OR]: 1.98, p < 0.001), DFS (OR: 2.12, p < 0.001), two-year survival (OR: 1.38, p =0.04) and five-year survival (OR: 2.16, p = 0.007) compared to surgery alone. • There was no statistically significant difference observed with regard to OS (OR: 0.99, p = 0.93), DFS (OR: 0.99, p = 0.95), and two-year survival (OR: 0.90, p = 0.57) between adjuvant chemoradiotherapy and surgery alone.	Ren et al, 2012
Adjuvant chemotherapy/ chemoradiotherapy Vs. Surgery alone	Patients with radically resected pancreatic cancer (N=2410)	12 RCTs	5-year-survival rate, NNT	• Low to moderate heterogeneity between the trials was documented both for AT (I2=29.8%, p=0.153) and AC (I2=48.2%, p=0.051), but not for ACR (I2=0%, p=0.773). • A significant improve in 5-year-survival rate was observed for AT and AC (odds ratio of 0.62, p=0.001 and 0.63, p=0.021 respectively), but not for ACR (odds ratio=0.92, p=0.71), with an 5-year survival NNT of 14 (p=0.001), 15 (p=0.021) and 125 (p=0.71) respectively for AT, AC and ACR	Drudi et al, 2011 (Abstract)

Adjuvant chemoradiotherapy Vs. Surgery alone	Patients with resectable pancreatic cancer (N=1507)	8 RCTs	OS	• Compared to the control group, the adjuvant chemoradiotherapy group had significantly higher 2- and 5-year survival rates (OR = 1.96, 95% CI (1.55, 2.48); OR = 1.89, 95% CI (1.41, 2.53)	Wang et al, 2011 (Abstract)
Adjuvant chemotherapy Vs. Surgery alone	Patients with early resectable pancreatic cancer (N=1019)	6 RCTS	OS and DFS	• A 4% relative increase was obtained in the 1-year OS rate (P = 0.4), and the relative increase was 8% in the 3-year OS rate (P = 0.001). The relative increase in the 5-year OS rate was 6% (P = 0.0009). However, there were no significant differences between the 1 and 5-year OS rate. • In terms of DFS, a 23% relative increase was obtained in the 1-year DFS rate (P < 0.00001), and the relative increase was 8% in the 3-year DFS rate (P = 0.006). The relative increase in the 5-year DFS rate was only 3% (P = 0.11). • No significant difference between the 5-year DFS of the two groups was found	Zeng et al, 2011 (Abstract)
Adjuvant chemotherapy + gemcitabine (GEM) Vs. Observation	Patients with resected pancreatic cancer (N=472)	2RCTs	PFS, OS	• The progression-free survival was higher in the group of patients who were treated with adjuvant chemotherapy including GEM (fixed effect: HR = 0.59, CI 95% = 0.50 to 0.70; P < 0.00001) and no heterogeneity was found (x^2= 0.01, df = 1 (P = 0.94); I2= 0%). • Overall survival was also higher in patients treated with GEM (fixed effect: HR = 0.81, CI 95% = 0.67 to 0.98; P = 0.03) yet again no heterogeneity was detected (x2=0.07, df=1 [P=0.79]; I^2=0%)	Botrel et al, 2010 (Abstract)
Adjuvant chemotherapy/ chemoradiotherapy Vs. Surgery alone	Patients with resected pancreatic cancer (N=951)	5 RCTs	OS	• The meta-analysis estimate for prolongation of median survival time for patients in the chemotherapy group was 3 months (95% CI 0.3–5.7 months, p = 0.03). • The difference in 5-year survival rate was estimated with 3.1% between the chemotherapy and the control group (95% CI –4.6 to 10.8%, p >0.05)	Boeck et al, 2007
Randomized control trials					
Interventions	**Population**	**Follow-up**	**Outcomes**	**Brief results**	**References**
Surgery alone (Arm A) Vs. Neoadjuvant CRT (55.4 Gy; gemcitabine &	Patients with histologically proven ductal adenocarcinoma of the pancreatic head and <180° contact to peri-pancreatic vessels	NR	Median OS	• Trial was closed early due to slow recruitment the • Postoperative complications were comparable in both groups. • Intention-to-treat mOS was 14.4 months (A) and 17.4 months (B) (p=n.s.).	Brunner et al, 2012 (Abstract)

cisplatin) + Surgery (Arm B)	(n=68)			• Analysis per protocol shows a median overall survival of 25 months in arm B versus 18 months in arm A for pts with resections (p=n.s.).	
Neoadjuvant chemoradiation (NAT) + Surgery (Group A) Vs. Surgery alone (Group B)	Patients with resectable pancreatic adenocarcinoma (n=16)	NR	**P:** R0 resection rate **S:** safety, efficacy, postoperative mortality, morbidity, and lymph node ratio.	• R0 resection rate: Group A 60% (3/5); Group B 11.1% (1/9) (P = 0.095). NAT morbidity rate: 80% (4/5). • One case (20%) after NAT had a progression of the disease, two cases had partial response (40%) and one had a stable disease (40%). • Surgical resection was performed in 4 patients of Group A (80%) and in 8 (88.8%) of Group B (1 case unresectable). • Overall postoperative mortality: 1/12 (8.3%) (Group A vs. Group B: P = 1.000) • Overall postoperative morbidity: 5/12 (41.7%) (0% Group A vs. 62.5% Group B, P = 0.081). • Mean number of lymph node metastasis was lesser (P = 0.051) in Group A (2±3) than in Group B (9±5)	D'Ambra et al, 2010 (Abstract)
Adjuvant Intra-operative Radiation Therapy (IORT) Vs. Surgery alone	Patients with potentially resectable advanced pancreatic Cancer (duct cell origin) by image diagnosis (n=198)	NR	**P:** OS **S:** Local control rate at 2 years after surgery	• 153 pts underwent curative resection with assigned treatment. • Among the 153 pts with curative resection, seven pts revealed ineligible by the histological examination. • Full Analysis Sets were 70 pts in the surgery alone arm and 74 pts in the IORT arm. • There was no survival benefit of adjuvant IORT for overall and relapse free survival and was no statistical difference in the local control of disease at 2 years in the two groups.	Kinoshita et al, 2009 & 2010 (Abstracts)
Adjuvant celiac axis infusion chemotherapy combined with radiotherapy (CAI/RT) Vs. Surgery Alone	Patients with resected pancreatic or periampullary cancer (n=120)	NR	QOL	• Eighty-six percent of patients (n=103) completed 1 or more questionnaires. • The results indicated that CAI/RT did not impair physical, emotional, or social functioning. During and after CAI/RT, patients had significantly less pain (P=.02) and less nausea and vomiting (P=.01). • Overall QoL (global functioning) tended to be better (P=.08) after CAI/RT.	Morak et al, 2010
Gemcitabine group vs. Surgery-only group	Patients who underwent macroscopically curative resection of	NR	**P:** OS **S:** DFS and gemcitabine safety	• Both groups were well balanced in terms of baseline characteristics. • Although heamatological toxicity was frequently observed in the gemcitabine group, most toxicities were transient,	Ueno et al, 2009

	pancreatic cancer (n=119)			and grade 3 or 4 non-heamatological toxicity was rare. • Patients in the gemcitabine group showed significantly longer disease-free survival (DFS) than those in the surgery-only group (median DFS, 11.4versus 5.0 months; hazard ratio=0.60 (95% confidence interval (CI): 0.40–0.89); P=0.01), although overall survival did not differ significantly between the gemcitabine and surgery-only groups (median overall survival, 22.3 versus 18.4 months; hazard ratio=0.77 (95% CI: 0.51–1.14); P=0.19).	
Adjuvant celiac axis infusion chemotherapy combined with radiotherapy (CAI/RT) Vs. Surgery Alone	Patients with resected pancreatic or periampullary cancer (n=120)	Median, 17 months	**P:** OS **S:** DFS and safety	• No significant OS benefit was seen (median, 19 vs. 18 months resp.). • Progressive disease was seen in 86 patients: in 37 patients in the CAI/RT group, and in 49 patients in the observation group (log-rank P < 0.02). • Subgroup analysis showed significantly less liver metastases after adjuvant treatment in periampullary tumors (log-rank P < 0.03) without effect on local recurrence. • Nonetheless, there was no significant effect on overall survival in these patients (log-rank P = 0.15). • In patients with pancreatic cancer, CAI/RT had no significant effect on local recurrence (log-rank P = 0.12) neither on the development of liver metastases (log-rank P =0.76) and consequently, no effect on OS.	Morak et al, 2008
Gemcitabine group (G) vs. Observation (O)	Patients with resected pancreatic cancer (n=368)	NR	**P:** DFS **S:** OS and Toxicity	• In JAMA 2007 first results showed that postoperative G is well tolerated and significantly delays the development of recurrent disease after complete resection of PC. • By December 1, 2007, 303 events (85.6%) have occurred for DFS and 293 events (82.8%) for OS. • The analyses confirm the significant improvement for G in median DFS [G: 13.4 months (m), O: 6.9m, p< 0.001]. • Estimated DFS at 3 and 5 years was 23.5% and 16.0% in the G group vs. 8.5% and 6.5% in the O group, respectively. • Subgroup analyses demonstrate significant increased DFS for G in all subgroups of stratification. • G significantly improves median OS [G:	Riess et al, 2008 (Abstract)

				22.8m, O: 20.2m, p=0.005]. • Estimated survival at 3 and 5 years was 36.5% and 21.0% for G pts vs. 19.5% and 9.0% for O pts, respectively.	

Ongoing trials
Retrieved from www.clinicaltrials.gov

Intervention	Official title	Status	Protocol ID	Completion Date	Last updated
Neoadjuvant Radiotherapy Vs. Surgery	Neoadjuvant Radiotherapy in Patients With Primary Resectable Adenocarcinoma of the Pancreatic Head Plus Adjuvant Chemotherapy: a Randomized Controlled Phase III Trial	Not yet recruiting	NCT01419002	April 2015	August 16, 2011

Abbreviations: PAC=Pancreatic Adenocarcinoma; OS=Overall survival; DFS=Disease free survival; Adjuvant treatments=AT; Chemotherapy=AC; Chemo-radiotherapy=ACR; Progression free survival=PFS; Chemoradiotherapy=CRT;

Clinical Expert Interest Declaration:

No COI declared

Instructions. 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. The recommendations stand, but the qualifying statements need revision. The statement which currently indicates that 5FU is a regimen with better evidence than gemcitabine is no longer correct. There is now equally strong evidence for the use of gemcitabine, including two Gem vs 5FU comparative trials which demonstrate both regimens are effective. Suggest changing from: "Trials comparing 5FU to gemcitabine in the postoperative setting are ongoing. The evidence for a survival benefit is more convincing for 5FU-based regimens." to: "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.
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new	a. Yes. The new evidence continues to support the existing recommendations. b. No. While the evidence review did not identify this topic, there is a trend emerging in some centres to delay the onset of radiation until after several months of adjuvant chemotherapy have been completed. This strategy may avoid excessive local treatment in the subset of patients with early distant recurrence,

recommendations are necessary?	while focussing efforts at improved local control in the remainder. A randomized phase II trial of gemcitabine alone versus gemcitabine followed by gemctitabine+RT [*Van Leathem et al JCO, Oct 2010*] demonstrated reduced local recurrence in the arm including delayed RT (11 vs 24%). This delayed RT strategy in patients free from early recurrence after 5 cycles of gemcitabine is now being evaluated in the RTOG 0848 study.
c. 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. To my knowledge, there are no imminently reporting randomized trials which might effect recommendations. Important ongoing trials which were not identified by the search criteria (because they didn't involve a surgery alone control arm) include the following: NCT01526135 UNICANCER / ACCORD24 /NCIC CTG PA.7 trial Multicentric Randomized Phase III Trial Comparing Adjuvant Chemotherapy With Gemcitabine Versus 5-fluorouracil, Leucovorin, Irinotecan and Oxaliplatin (mFolfirinox) in Patients With Resected Pancreatic Adenocarcinoma NCT01013649 NCI / US Intergroup trial: RTOG-0848 A Phase III Trial Evaluating Both Erlotinib and Chemoradiation as Adjuvant Treatment for Patients With Resected Head of Pancreas Adenocarcinoma NCT00960284 IRCCS (Italian research group) Randomized Phase II-III Trial of Post-operative Treatment of Pancreatic Adenocarcinoma: Gemcitabine Versus PEFG Followed by Radiochemotherapy With Concomitant Continuous Infusion of 5-fluorouracil (PACT-7) NCT01150630 IRCCS (Italian research group) Randomized Phase II-III Trial of Peri- or Post-Operative Chemotherapy [Gemcitabine, Cisplatin, Epirubicin, and Capecitabine (PEGX)] in Patients With Stage I-II Resectable Pancreatic (PACT-15) • 3 arm study of post-op Gem vs post-op PEGX vs Pre+post-op PEGX NCT01314027

	NCT01521702 Adjuvant Gemcitabine Versus NEOadjuvant Gemcitabine/Oxaliplatin Plus Adjuvant Gemcitabine in Resectable PAncreatic Cancer: a Randomized Multicenter Phase III Study (NEOPAC Study) • Neoadj GemOx then surgery then adj Gem vs Surgery then adj Gem
d. 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?	No. Full update of this document is neither currently required, nor of sufficient priority.

Review Outcome	Endorse
DSG/GDG Approval Date	April 2, 2013
DSG/GDG Commentary	None

New References Identified (alphabetic order):

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13. Wang SL, Lin Y, Gao S, Hu TY, Wu R. Efficacy of adjuvant chemoradiotherapy in pancreatic cancer patients after surgical resection:A meta-analysis. World Chinese Journal of Digestology. 2011;19(31):3272-6.
14. Zeng W, Zhang X. Meta-analysis of the long-term efficacy of adjuvant chemotherapy and surgery-only for resectable pancreatic cancer. [Chinese]. Chinese Journal of Clinical Oncology. 2011;38(21):1346-50.

Search strategy:

Medline

1. meta-Analysis as topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s 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 psyclit 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 bibliograph$ 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. (randomi$ 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 random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. exp pancreatic neoplasms/
42. (adjuvant or neoadjuvant).tw.
43. Pancreatic Neoplasms/ or pancreatic adenocarcinoma.mp. or Carcinoma, Pancreatic Ductal/
44. 41 or 43
45. 42 and 44
46. (200746: or 2008: or 2009: or 2010: or 2011: or "2012").ed.
47. 45 and 46
48. (resec$ or resect$ or resection or resectable).tw.
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 synthes?s 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. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit 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$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. exp pancreatic neoplasms/
37. pancreatic adenocarcinoma.mp. or exp pancreas adenocarcinoma/
38. 36 or 37
39. (adjuvant or neoadjuvant).tw.
40. 38 and 39
41. (200746$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$).ew.
42. 40 and 41
43. (resec$ or resect$ or resection or resectable).tw.
44. 42 and 43

ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: Resectable Pancreatic Adenocarcinoma

Clinicaltrials.gov – searched http://clinicaltrials.gov/ct2/home with keywords: Resectable Pancreatic Adenocarcinoma

OUTCOMES DEFINITION

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 our website, 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. **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.