

# The treatment of locally advanced pancreatic cancer: A practice guideline

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**BACKGROUND:** Pancreatic adenocarcinoma is the fourth most common cause of adult cancer death. About 50% of patients present with metastatic disease, 20% with resectable disease and the remaining 30% of patients are diagnosed with incurable, locally advanced unresectable but nonmetastatic pancreatic cancer.

**OBJECTIVES:** To evaluate the current evidence regarding treatment of incurable, locally advanced, unresectable but nonmetastatic pancreatic cancer and produce an evidence-based practice guideline.

**METHODS:** A systematic review of the literature was performed. The MEDLINE, CANCELIT, and Cochrane Library databases were searched using the following medical subject heading search terms: 'pancreatic neoplasms', 'chemotherapy, adjuvant', 'radiotherapy', 'immunotherapy', combined with the text words: 'chemotherapy', 'radiotherapy', 'radiation', 'immunotherapy', combined with terms for the following study designs or publication types: practice guidelines, meta-analyses and randomized controlled trials. The Physician Data Query clinical trials database and the proceedings of the annual meetings of the American Society of Clinical Oncology (1996 to 2001) and the American Society for Therapeutic Radiology and Oncology (1999 to 2001) were searched for reports of new or ongoing trials. Relevant literature was selected and reviewed independently, and the reference lists from these sources were searched for additional trials. Interpretation of evidence was resolved by consensus.

**RESULTS:** Eight randomized trials were obtained that met the inclusion criteria.

**CONCLUSIONS:** Recommendations are to offer combined chemotherapy and radiotherapy to suitable patients. The preferred chemotherapeutic agent to combine with radiotherapy is bolus or infusional 5-fluorouracil, but the optimal mode and duration of 5-fluorouracil delivery is unclear. Chemotherapy alone with gemcitabine is an acceptable alternative.

**Key Words:** *Advanced pancreatic cancer; Practice guideline; Treatment*

## Traitement d'un cancer du pancréas, évolué localement : directives cliniques

**CONTEXTE :** L'adénocarcinome du pancréas est la quatrième cause de mortalité par cancer chez les adultes. Environ 50 % des patients ont des métastases, 20 % sont opérables et 30 % présentent un cancer incurable, évolué localement, non résécable mais non métastatique.

**OBJECTIFS :** Évaluer les données actuelles en ce qui concerne le traitement du cancer du pancréas incurable, évolué localement, non résécable mais non métastatique et formuler des directives cliniques fondées sur des preuves.

**MÉTHODE :** Nous avons procédé à un examen systématique de la documentation et avons consulté les bases de données MEDLINE, CANCELIT et Cochrane Library à l'aide des vedettes-matière suivantes : « pancreatic neoplasms », « chemotherapy adjuvant », « radiotherapy », « immunotherapy »; des mots-de-texte suivants : « chemotherapy », « radiotherapy », « radiation », « immunotherapy » et des termes suivants relativement aux types d'étude et aux types de publication : « practice guidelines », « meta-analyses » et « randomized controlled trials ». Nous avons également consulté la base de données Physician Data Query sur les essais cliniques ainsi que les actes des congrès annuels de l'American Society of Clinical Oncology (1996 à 2001) et de l'American Society for Therapeutic Radiology and Oncology (1999 à 2001) à la recherche de rapports de nouveaux essais ou d'essais en cours. Il y a eu sélection de la documentation pertinente, réexamen de la matière par des autorités indépendantes et recherche supplémentaire à partir des listes de références données dans les sources retenues. L'interprétation des données s'est faite par consensus.

**CONCLUSION :** Les recommandations consistent à offrir et la chimiothérapie et la radiothérapie aux patients dont l'état se prête au double traitement. L'agent chimiothérapeutique à privilégier est le 5-fluorouracile en bolus ou en perfusion, mais la durée et le mode d'administration optimaux restent encore à préciser. La chimiothérapie seule à la gemcitabine offre une solution de rechange acceptable.

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**A**denocarcinoma of the exocrine pancreas is the fourth most common cause of cancer death in adults (1,2). Smoking and a history of chronic pancreatitis are established risk factors, and data are emerging to support occasional inherited susceptibilities, as well as increased risk from a high-fat diet (3). It is highly lethal, with only 5% of patients alive at five years. About 50% of patients present with metastatic disease and have a median survival time of less than six months, with a one-year survival rate of less than 20% (2). Twenty per cent present with localized resectable disease, and up to one-quarter of these patients can be cured with surgery (4), with adjuvant chemoradiotherapy possibly increasing the cure rate (5). The remaining 30% of patients are diagnosed with incurable, locally advanced, unresectable but nonmetastatic pancreatic cancer.

Resection of locally advanced pancreatic cancer is usually not possible because of invasion of the portal or superior mesenteric vessels, splenic vein thrombosis or metastases to second level lymph nodes. Patients have a median survival time of six to 10 months and a one-year survival rate of 20% to 40% (6-15). Several clinical trials have explored the value of chemotherapy and/or radiotherapy in this group of patients. A systematic review of this literature and a practice guideline on the topic are therefore warranted. The practice guideline was intended to make recommendations regarding the optimal treatment for patients with locally advanced (unresectable but nonmetastatic) pancreatic cancer. Outcomes of interest were overall survival, disease-free survival, local control, adverse effects and quality of life.

## METHODS

### Guideline development

This practice guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) using the methodology of the Practice Guidelines Development Cycle (16). Evidence was selected and reviewed by three members of the CCOPGI's Gastrointestinal Cancer Disease Site Group (DSG) and methodologists. Members of the Gastrointestinal Cancer DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the treatment of locally advanced pancreatic cancer, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The report is intended to enable evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

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

### Literature search strategy

MEDLINE (January 1966 to March 2002), CANCERLIT (January 1983 to October 2001), and the Cochrane Library (2002, Issue 1) were searched with no language restrictions. 'Pancreatic neoplasms' (Medical subject heading [MeSH]) was combined with 'chemotherapy, adjuvant' (MeSH), 'radiotherapy' (MeSH), and 'immunotherapy' (MeSH), and each of the following phrases used as text words: 'chemotherapy', 'radiotherapy', 'radiation', and 'immunotherapy'. These terms were then combined with the

search terms for the following study designs or publication types: practice guidelines, meta-analyses and randomized controlled trials. The Physician Data Query clinical trials database on the Internet ([http://www.nci.nih.gov/search/clinical\\_trials/](http://www.nci.nih.gov/search/clinical_trials/)) and the proceedings of the 1996 to 2001 annual meetings of the American Society of Clinical Oncology and the 1999 to 2001 annual meetings of the American Society for Therapeutic Radiology and Oncology were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by each reviewer independently, and the reference lists from these sources were searched for additional trials.

### Inclusion criteria

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

### Exclusion criteria

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

### Synthesizing the evidence

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

## RESULTS

### Literature search results

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

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

A trial by Burris et al (17) comparing gemcitabine to 5-fluorouracil (5-FU) in the treatment of advanced pancreatic cancer did not meet the eligibility criteria for inclusion in this systematic review because the results for patients with locally advanced disease were not reported separately; however, this trial is included in the discussion in the DSG consensus process section.

**TABLE 1**  
**Randomized trials in locally advanced pancreatic cancer**

Reference	Radiation (Gy)	Chemotherapy	Number of patients randomized (evaluable)	Median Survival (months)	Percentage one-year survival (estimate*)
<b>A) Chemoradiotherapy versus radiotherapy alone</b>					
Moertel et al, 1969 (6)	35-40	5-FU	NR (32)	10.4 <sup>†</sup>	NR (25 <sup>†</sup> )
	35-40	Placebo	NR (32)	6.3	NR (6)
				(mean)	
GITSG 9273, 1981 (7-9)	60	5-FU	111 (86)	11.4	44 <sup>†</sup>
	40	5-FU	117 (83)	8.4	39 <sup>†</sup>
	60	—	25 (25)	5.3	14
<b>B) Chemoradiotherapy versus chemotherapy alone</b>					
ECOG, 1985 (10)	40	5-FU	NR (47)	8.3	NR (28)
	—	5-FU	NR (44)	8.2	NR (31)
GITSG 9283, 1988 (11)	54	5-FU + SMF	24 (22)	9.7 <sup>†</sup>	41 <sup>†</sup>
	—	SMF	24 (21)	7.4	19
<b>C) Chemoradiotherapy with comparison of different chemotherapy regimens</b>					
SWOG, 1980 (12)	60	mCCNU+5-FU	NR (33)	8.8	NR (40)
	60	mCCNU+5-FU+testolactone	NR (29)	6.9	NR (27)
GITSG 9277, 1985 (13)	60	5-FU	79 (73)	8.5	NR (33)
	40	doxorubicin	78 (70)	7.6	NR (26)
Earle et al, 1994 (14)	50-60	5-FU	44 (44)	7.8	NR (34)
	50-60	Hycanthone	43 (43)	7.8	NR (26)
<b>D) Comparison of different types of radiation beams</b>					
RTOG, 1989 (15)	photons	—	23 (23)	8.3	17
	mixed	—	11 (11)	7.8	10
	neutrons	—	15 (15)	5.6	8

\*Calculated from survival curve where data not provided in the text; <sup>†</sup>P<0.05. 5-FU Bolus 5-fluorouracil; ECOG Eastern Cooperative Oncology Group; GITSG Gastrointestinal Tumor Study Group; Gy Gray; mCCNU Methyl lomustine; NR Not reported; RTOG Radiation Therapy Oncology Group; SMF Streptozocin, mitomycin, 5-FU; SWOG Southwest Oncology Group

## Outcomes

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

The Gastrointestinal Tumour Study Group (GITSG) undertook a three-arm study of 60 Gy double-split radiotherapy with two, two-week rest periods compared with the same radiation dose combined with 5-FU, or 40 Gy single-split course with 5-FU (7-9) (Table 1[A]). In the chemotherapy-containing arms, 5-FU was given at a dose of 500 mg/m<sup>2</sup> intra-

venously (IV) on the first three days of each 20 Gy of radiation, and then continued as a weekly bolus infusion for two years. The radiation-alone arm was stopped after only 25 patients had been enrolled because it had become clear that both the median survival time and the one-year survival rate were half those in the chemotherapy-containing arms (P<0.01). There was no significant survival difference between the two combined-modality arms, although there was a nonsignificant trend toward prolonged time to progression (P=0.14) and improved survival (P=0.19) for 60 Gy over 40 Gy, suggesting a dose-response relationship. However, the nonstatistically significant advantage for the 60 Gy over the 40 Gy arm did not result in longer term survival as evidenced by the survival curves overlapping at 15 months. Local failure was a component of progression in about 25% of patients. Toxicity mostly consisted of nausea/vomiting and leucopenia, which occurred in all groups. Severe toxicity (up to 5% of patients) and mucositis occurred only in patients receiving 5-FU.

**Chemoradiotherapy versus chemotherapy:** There were two randomized trials of chemoradiotherapy compared with chemotherapy alone (10,11) (Table 1[B]). A study by the Eastern Cooperative Oncology Group (ECOG) (10) suggested that 5-FU alone was as effective as combined therapy with 5-FU and radiation. 5-FU was given at a dose of 600 mg/m<sup>2</sup> weekly until disease progression. Chemoradiotherapy consisted of 5-FU 600 mg/m<sup>2</sup> IV on the first three days of radiation, which was administered to a total dose of 40 Gy. Patients

receiving chemoradiotherapy were given maintenance 5-FU afterwards, as administered in the chemotherapy arm. The trial closed early due to poor accrual, with 91 pancreatic cancer patients enrolled (patients with gastric cancer were also included). The median time to treatment failure for the patients with pancreatic cancer was 4.4 months with 5-FU versus 4.2 months with chemoradiotherapy (P-value not reported). There was more toxicity (leucopenia accompanied by sepsis) in patients receiving combined-modality treatment. There was no difference in local control between the arms. The results of this study have been questioned because of the poor survival seen in both arms, the less than optimal radiation planning and delivery in the radiation arm, the brevity of the course of chemotherapy in the combined-modality arm compared with other studies, and the possibility that the observed survival equivalence is a power issue due to poor accrual and early closure.

In 1988, the GITSG reported a randomized controlled trial evaluating multidrug chemotherapy with streptozocin 1 g/m<sup>2</sup> day 1, mitomycin-C 10 mg/m<sup>2</sup> day 1, and 5-FU 600 mg/m<sup>2</sup> (SMF) on days 1, 8, 29, and 36 given in eight-week cycles for two years, or until disease progression, versus 54 Gy of radiation given with 5-FU 350 mg/m<sup>2</sup>/day on the first three and last three days of radiotherapy (11) (Table 1[B]). According to the Nominal Standard Dose concept of Orton and Ellis (18), the single course of 54 Gy was considered to be radiotherapeutically equivalent to the 60 Gy double-split regimens used in earlier studies by the GITSG. Following radiation, patients were given SMF for up to two years. The study was closed early due to lack of funding with only 24 patients in each arm. Overall survival was significantly better with combined-modality treatment (median survival 42 weeks, 41% at one year) compared with chemotherapy alone (median survival 32 weeks, 19% at one year) (P<0.02). At 18 months, 18% of patients in the combined-modality arm were alive, but none were alive in the SMF-only arm. Severe toxicity was experienced by 50% of patients in the chemoradiotherapy group, with life-threatening leucopenia in four patients and life-threatening thrombocytopenia in one patient. There were no life-threatening adverse effects in the SMF-only arm. The GITSG results have been questioned because the study closed after accruing only 24 patients in each arm due to lack of funding. Therefore, any observed difference could be attributed to a statistical power issue caused by inadequate accrual, not any treatment effect.

**Chemoradiotherapy comparing different chemotherapeutic agents:** Three randomized trials of chemoradiotherapy evaluated different chemotherapeutic agents (12-14) (Table 1[C]). The Southwest Oncology Group randomly allocated 69 patients to 60 Gy of radiation with methyl lomustine 125 mg/m<sup>2</sup> orally every six weeks and 5-FU 400 mg/m<sup>2</sup> weekly, with or without testalactone 200 mg orally daily (12). Survival was similar in each arm (P=0.68). Among 62 evaluable patients, the most common adverse effects were myelosuppression (87%) and gastrointestinal toxicity (23%), and there was one treatment-related death associated with granulocytopenia.

The GITSG compared 5-FU given with 60 Gy of radiation in a double-split course, with doxorubicin 15 mg/m<sup>2</sup> on day 1 followed by 10 mg/m<sup>2</sup> weekly given with 40 Gy of radiation administered in a continuous course (13) (Table 1[C]). After radiation, the doxorubicin was continued on a three to four week schedule until the maximum safe dose had been given, at which time patients were switched to 5-FU. A total of 143 patients were analyzed, and there was no significant survival

difference. However, toxicity was significantly increased for patients receiving doxorubicin, with more patients suffering from hematological toxicity, mucositis and diarrhea. Additionally, the sole treatment-related death occurred in the doxorubicin arm due to a perforated viscus. Both arms found some palliation of pain in about one-third of the patients. However, over half of the patients in both arms had local disease progression as their initial site of progression.

A randomized phase II study compared the radiation sensitizer hycanthone, given at 60 mg/m<sup>2</sup> IV on days 1 through 5 and days 29 through 33, with standard 5-FU given at 500 mg/m<sup>2</sup> for the first three days of each of three 20 Gy split radiation courses (total dose 60 Gy) (14) (Table 1[C]). There was no difference in survival (P=0.82) or disease-free survival (P=0.27). Furthermore, hycanthone was associated with hepatic toxicity that resulted in one death.

**Chemoradiotherapy comparing different types of radiation beams:** The Radiation Therapy Oncology Group randomized 49 evaluable patients to receive radiation treatment that was radiotherapeutically equivalent to 64 Gy of photon radiation treatment. Either pure photons or neutrons, or a combination (mixed-beam irradiation) of both, were used (15) (Table 1[D]). Neutron irradiation was postulated to have several advantages due to its high linear energy transfer properties and, thus, the possibility of improved local control. In this poorly powered study, there were no statistically significant differences in survival or local control among the arms. Median disease-free survival was also similar among treatment groups: 3.7 months with neutron irradiation, 3.4 months with mixed radiation beams and 3.7 months with pure photon irradiation. However, three neutron-irradiated patients suffered moderate to life-threatening gastrointestinal toxicity compared with one patient treated with photons.

**Adverse effects of chemoradiotherapy:** Chemoradiotherapy can be associated with cytopenia, nausea, vomiting and diarrhea (6-11) (Table 2). However, these adverse effects are generally tolerable, and treatment-related deaths are unusual. Combination 5-FU and radiation is also well tolerated. Although not superior to 5-FU in efficacy, other chemotherapeutic regimens appear to be more toxic (13,14).

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

## DISCUSSION

Three randomized trials have shown chemoradiotherapy to be superior to either chemotherapy alone or radiation alone in terms of improved survival (6-9,11). Among three randomized trials of chemoradiotherapy comparing different chemotherapeutic agents, no chemotherapy regimen was superior to 5-FU in combination with radiation (12-14). These data support the use of chemoradiotherapy as standard practice for medically suitable patients. Outside of a clinical trial, 5-FU is the preferred chemotherapeutic agent to combine with radiotherapy, however, the optimal mode and duration of 5-FU delivery is unclear. Although different from the regimens actually used in the trials, common protocols give 5-FU either by continuous infusion at a dose of 200 mg/m<sup>2</sup>/day during radiation, or bolus injection of 500 mg/m<sup>2</sup>/day on days 1 through 3 and the last three days of



**TABLE 2**  
**Adverse effects of treatment**

Reference	Treatment Arm	Nausea or vomiting (%)	Adverse effects – all grades			Treatment-related deaths
			Diarrhea (%)	Leucopenia (%)	Thrombocytopenia (%)	
A) Chemoradiotherapy versus radiotherapy alone						
Moertel et al, 1969 (6)	RTCT (5-FU)	76	13	100	52	NR
	RT alone	40	6	31	7	NR
GITSG 9273, 1981 (7-9)	RTCT (60 Gy + 5-FU)	86	7	78	37	NR*
	RTCT (40 Gy + 5-FU)	77	6	62	45	1
	RT alone (60 Gy)	64	0	52	8	NR*
B) Chemoradiotherapy versus chemotherapy alone						
ECOG, 1985 (10)	RTCT (5-FU)	NR	NR	17	NR	NR
	CT (5-FU)	NR	NR	2	NR	NR
				P<0.05		
GITSG 9283, 1988 (11)	RTCT (5-FU+SMF)	78	46	100	100	NR
	CT (SMF)	95	48	100	100	NR
C) Chemoradiotherapy with comparison of different chemotherapy regimens						
SWOG, 1980 (12)	RTCT (mCCNU+5-FU)	Did not report adverse effects separated by treatment arm (%)				
	RTCT (mCCNU+5-FU)					
	CT (testalactone).					
GITSG 9277, 1985 (13)	RTCT (5-FU)				36	0
	RTCT (doxorubicin)				53	1
					P<0.05	
Earle et al, 1994 (14)	RTCT (5-FU)	90	0	50	NR	0
	RTCT (hycanthone)	90	2	0	NR	1
			Grade 3+	<2000 mm <sup>3</sup>		
D) Comparison of different types of radiation beams						
RTOG, 1989 (15)	Photons	9	0	0		NR
	Mixed	9	0	0		NR
	Neutrons	6	6	0		NR
		Grade 3+	Grade 3+	(all adverse hematological effects)		

\*Two other patient deaths noted in report, treatment arm unspecified. 5-FU Bolus 5-fluorouracil; CT Chemotherapy; ECOG Eastern Cooperative Oncology Group; GITSG Gastrointestinal Tumor Study Group; Gy Gray; mCCNU Methyl lomustine; NR Not reported; RT Radiotherapy; RTCT Chemoradiotherapy; RTOG Radiation Therapy Oncology Group; SMF Streptozocin, mitomycin, 5-FU; SWOG Southwest Oncology Group

radiation, usually without subsequent maintenance treatment. This practice guideline does not make a recommendation for bolus 5-FU infusion over continuous 5-FU infusion despite the fact that the majority of the studies examined used bolus infusion as the treatment modality of choice. However, there is empirical evidence showing an enhancement of radiotherapy effects with continuous 5-FU infusion compared with bolus 5-FU infusion (19). Consequently, for any positive benefit that is seen with bolus 5-FU infusion, at least equivalent or greater benefit can be expected with continuous 5-FU infusion. The dose of radiation treatment ranges from 45 Gy to 54 Gy, given at 1.8 Gy per fraction over five to six weeks.

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

There are a number of ongoing North American trials examining the use of chemotherapy alone and/or combination chemoradiotherapy treatment in pancreatic cancer. Several of these studies (protocol identification numbers CAN-NCIC-

PA3, CWRU-010224M, and CPMC-IRB-8544) list quality of life as an outcome of interest, and this information will be made available upon publication.

### DSG consensus process

The Gastrointestinal Cancer DSG reached consensus on the draft guideline recommendations, with the following item being discussed. Because the evidence for radiation is relatively weak, there was discussion around whether treatment with gemcitabine alone should be presented as an equally acceptable alternative. The only randomized data on gemcitabine is the study by Burris et al (17), which demonstrated that gemcitabine improves symptoms and modestly improves survival compared with 5-FU as single-agent chemotherapy in patients with locally advanced or metastatic pancreatic cancer. These patients were symptomatic, had a life expectancy of at least 12 weeks, and a Karnofsky performance status of at least 50% (equivalent to an ECOG performance status of less than three). This randomized trial is discussed in detail in another guideline (20) developed by the Gastrointestinal Cancer DSG, which concludes that gemcitabine is a reasonable treatment option for patients with locally advanced or metastatic pancreatic cancer. Twenty-six per cent of the patients included in the randomized trial by Burris et al (17) had locally advanced disease but they were not reported separately, and attempts to

**TABLE 3**  
**Practice guideline**

Target population	These recommendations apply to adult patients with locally advanced (unresectable but nonmetastatic) adenocarcinoma of the exocrine pancreas
Recommendations	The intent of treatment of locally advanced pancreatic cancer is palliation in symptomatic patients and prolongation of life in medically suitable cases
Key recommendations	Recommendations are to offer combined chemotherapy and radiotherapy to suitable patients who desire treatment Outside of a clinical trial, 5-fluorouracil (5-FU) given as bolus or infusion is the preferred chemotherapeutic agent to combine with radiotherapy. The optimal mode and duration of 5-FU delivery is unclear
Qualifying statements	Specific anticancer treatments (such as resection, chemotherapy and radiation) may be supplemented with supportive care (such as pain control, nutritional support, biliary stenting and bowel decompression as needed) if appropriate The evidence on which current conventional practice is based is relatively weak Chemotherapy alone with gemcitabine is an acceptable alternative

obtain the original data on these patients were unsuccessful. However, because the overall results detected a benefit with gemcitabine, the Gastrointestinal Cancer DSG inferred that patients with locally advanced disease unable to undergo radiation may be appropriately treated as having metastatic disease.

#### Practitioner feedback

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

**Results:** Ninety-four surveys (64%) were returned. Forty-eight respondents (51%) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey. Seventeen respondents (35%) provided written comments. The main points contained in the written comments were that the survival benefit of 5-FU plus radiotherapy is modest and may not be worth the complications, that gemcitabine may be a reasonable alternative to 5-FU plus radiotherapy, and that gemcitabine data be presented in the results. Another stated that symptomatic care only should be included as one of the alternative recommendations.

**Modifications and/or actions:** The only randomized data on gemcitabine are in the study by Burris et al (17), and this trial is discussed in detail in another guideline developed by the

Gastrointestinal Cancer DSG, which addresses the use of gemcitabine for the treatment of advanced pancreatic cancer (20). Some patients with locally advanced disease were included in the trial by Burris et al (17), but the results for these patients were not reported separately. For this reason, data on gemcitabine were not included in the Results section of the present guideline report, but this information is included in the Discussion instead. See Table 3 for practice guideline.

#### Related guidelines

Cancer Care Ontario Practice Guideline Initiative's Practice Guideline Report #2-10: Use of Gemcitabine in the Treatment of Advanced Pancreatic Adenocarcinoma can be found on the internet at [http://www.ccopecbc.ca/guidelines/gas/cpg2\\_10.html](http://www.ccopecbc.ca/guidelines/gas/cpg2_10.html). Additionally, a guideline to address the topic of supportive and symptomatic care in the treatment of locally advanced pancreatic cancer has been identified as a future topic by the Gastrointestinal Cancer DSG.

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