Ontario Health
Cancer Care Ontario

Guideline 2-33 IN REVIEW

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

Role of Adjuvant Treatment in Resected Pancreatic Ductal Adenocarcinoma

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An assessment conducted in December 2024 placed Guideline 2-33 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 2-33 is comprised of 5 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/71976

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Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To make recommendations regarding the adjuvant treatment (adjuvant chemotherapy, adjuvant chemoradiation therapy [CRT] and adjuvant stereotactic body radiation therapy [SBRT]) of patients with resected pancreatic ductal adenocarcinoma (PDAC) with respect to overall survival, progression-free survival, toxicity/safety, and quality of life.

TARGET POPULATION

These recommendations apply to adults with resected PDAC with R0 or R1 margins who are eligible for adjuvant treatment. This guideline does not apply to patients being considered for neoadjuvant therapy of PDAC.

INTENDED USERS

The intended users of this guideline are clinicians involved in the delivery of care to patients with resected PDAC.

RECOMMENDATIONS

Recommendation 1
Adjuvant chemotherapy is recommended for patients with R0 or R1 resected pancreatic ductal adenocarcinoma. Modified FOLFIRNOX (mFOLFIRINOX) is recommended for appropriately fit patients. If a patient is not suitable for mFOLFIRINOX, alternative options include gemcitabine plus capecitabine or gemcitabine alone.

Recommendation 2
There is insufficient evidence to support the routine use of adjuvant chemoradiation for patients with R0 or R1 resected PDAC. The role for adjuvant CRT remains uncertain.

Recommendation 3
Following surgical resection of pancreatic cancer, adjuvant SBRT is only recommended on a clinical trial or multi-institutional registry. (Endorsed from the American Society for Radiation Oncology [ASTRO] guideline by Palta et al. 2019) (1).

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Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To make recommendations regarding the adjuvant treatment (adjuvant chemotherapy, adjuvant chemoradiation therapy [CRT] and adjuvant stereotactic body radiation therapy [SBRT]) of patients with resected pancreatic ductal adenocarcinoma (PDAC) with respect to overall survival (OS), progression-free survival (PFS), toxicity/safety, and quality of life (QOL).

TARGET POPULATION

These recommendations apply to adults with PDAC with R0 or R1 margins who are eligible for adjuvant treatment. This guideline does not apply to patients being considered for neoadjuvant therapy of PDAC.

INTENDED USERS

The intended users of this guideline are clinicians involved in the delivery of care to patients with resected PDAC including but not limited to hepato-pancreato-biliary surgeons, medical oncologists, and radiation oncologists.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1
Adjuvant chemotherapy is recommended for patients with R0 or R1 resected pancreatic ductal adenocarcinoma. Modified FOLFIRNOX (mFOLFIRINOX) is recommended for appropriately fit patients. If a patient is not suitable for mFOLFIRINOX, alternative options include gemcitabine plus capecitabine or gemcitabine alone.
Qualifying Statements for Recommendation 1
• All patients who have had a R0 or R1 PDAC resection should be assessed for adjuvant chemotherapy by a medical oncologist. • All adjuvant chemotherapy options should be discussed with each patient. • Adjuvant treatment can be delayed to allow patients adequate time to recover from surgery. Data from ESPAC-3 demonstrate that there is no difference survival outcomes if adjuvant chemotherapy is delayed by up to 12 weeks (2). • Data from ESPAC-4 demonstrate that R status was not significantly associated with local recurrence, distant recurrence, or death without recurrence (3). • The JASPAC-01 trial was limited to a Japanese population. Results of trial using the agent S-1 are not considered applicable to Western populations.
Key Evidence for Recommendation 1
• Two systematic reviews with network meta-analyses were retained (4, 5). Parmar et al. (4) was comprised of 10 publications of 11 important randomized controlled trials (RCTs) that included 4920 participants. Five RCTs compared an adjuvant chemotherapy to observation; CONKO-001 (6), JSAP-02 (7), ESPAC-3 (v1) (8), ESPAC-1 Plus (8), and ESPAC-1 (9). Six RCTs compared two different adjuvant chemotherapy regimens: APACT (10), PRODIGE (11), ESPAC-4 (12), CONKO-005 (13), JASPAC-01 (14), and ESPAC-3 (15).

- Direct pairwise meta-analysis comparing adjuvant chemotherapy with observation demonstrated significantly better disease-free survival (DFS) (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.46 to 0.68; p<0.00001) and OS (HR, 0.73; 95% CI, 0.63 to 0.84; p<0.00001) with adjuvant chemotherapy.
- Direct pairwise meta-analysis comparing other adjuvant chemotherapy regimens with gemcitabine alone demonstrated significantly better DFS (HR, 0.76; 95% CI, 0.63 to 0.92, p=0.005) and OS (HR, 0.72; 95% CI, 0.61 to 0.86, p=0.0002) for adjuvant chemotherapy.
- Indirect comparisons using network meta-analysis demonstrated that DFS was significantly improved with mFOLFIRINOX or S-1 compared with 5-fluorouracil (5-FU), gemcitabine, gemcitabine plus capecitabine, gemcitabine plus erlotinib and gemcitabine plus nab-paclitaxel.
- Indirect comparisons using network meta-analysis demonstrated that OS was significantly improved with mFOLFIRINOX compared with 5-FU, gemcitabine, and gemcitabine plus erlotinib but not gemcitabine plus capecitabine or gemcitabine plus nab-paclitaxel.
- The Kamarajah et al. (5) systematic review was almost identical to Parmar et al. (4) in dates covered, included studies and conclusions.

Justification for Recommendation 1

In this target population the beneficial effects of improved survival were considered to be clinically meaningful and outweighed the adverse effects of treatment toxicity. The benefits are considered to be substantially greater than the harms and the evidence is generalizable to the entire target population. Moreover, the certainty of the evidence is high. Therefore, the Working Group made a strong recommendation in favour of adjuvant chemotherapy. The Working Group members believed this recommendation would be acceptable and feasible to all stakeholders. Advocating for a referral to medical oncology, for all patients who have had an R0 or R1 resection, should improve equity in terms of access to care for all patients. Some of the essential supportive measures, which are provided concomitantly for patients receiving chemotherapy, and triplet chemotherapy in particular, may not be fully established or funded in some Ontario jurisdictions. There is, thus, the potential for inequities to exist for some patients who many not be able to afford the out-of-pocket expenses to acquire these supportive measures.

Recommendation 2

There is insufficient evidence to support the routine use of adjuvant chemoradiation for patients with R0 or R1 resected PDAC. The role for adjuvant CRT remains uncertain.

Qualifying Statements for Recommendation 2

- Whether there is a role for adjuvant CRT in the presence of positive margins and/or node-positive disease may be discussed on a case-by-case basis in the setting of a multidisciplinary case conference and a discussion with the patient outlining the risk and benefits of treatment.

Key Evidence for Recommendation 2

- One systematic review with network meta-analysis was retained (16). For the purposes of the current guideline only the trial data dealing with CRT were considered: Regine et al. (17), EORTC 40891 (18), ESPAC-1 (9), and Kalser et al. (19).
- There was no significant difference between fluorouracil and fluorouracil plus CRT with respect to one-year survival (HR, 1.07; 95% CI, 0.44 to 2.53), three-year survival (HR, 1.28; 95% CI, 0.64 to 2.46) and five-year survival (HR, 1.88; 95% CI, 0.60 to 7.02).
- There was no significant difference between gemcitabine and gemcitabine plus CRT with respect to one-year survival (HR, 0.86; 95% CI, 0.20 to 3.59), three-year survival (HR, 0.93; 95% CI, 0.33 to 2.57) and five-year survival (HR, 1.77; 95% CI, 0.30 to 11.98).
- Evidence that radiotherapy may play a role in patients with high-risk features of margin-positive (R1) resection and node-positivity is limited to subgroup analyses of larger trials.

Justification for Recommendation 2

In this target population the beneficial effects of improved survival have not been consistently demonstrated, and there is evidence of adverse effects with respect to treatment toxicity that is generalizable to the entire target population. Moreover, the clinical benefits and potential toxicities of CRT in the setting of these newer chemotherapy regimens are unknown. The certainty of the evidence is low owing to the lack of evidence with newer chemotherapy regimens. Direct evidence in the high-risk R1 and node-positive subgroups remains limited. Therefore, the Working Group members believed there was insufficient evidence to recommend routine adjuvant CRT at this time. The Working Group believed this recommendation would be acceptable and feasible to all stakeholders and would likely have no effect on equity.

Recommendation 3
Following surgical resection of pancreatic cancer, adjuvant SBRT is only recommended on a clinical trial or multi-institutional registry. (Endorsed from the American Society for Radiation Oncology [ASTRO] guideline by Palta et al. 2019) (1).
Qualifying Statements for Recommendation 3
• None.
Key Evidence for Recommendation 3
• One systematic review with network meta-analysis was retained (1) and the recommendation regarding SBRT was endorsed. All members of the ASTRO guideline Working Group agreed with this recommendation.
Justification for Recommendation 3
In this target population the beneficial effects of improved survival with SBRT were considered to be unknown. The balance between benefits and harms are considered to be unknown. The certainty of the evidence is low owing to a lack of good-quality data. Therefore, the Working Group members believed that it was appropriate to endorse the ASTRO recommendation that SBRT should only be use within the context of a clinical trial or multi-institutional registry. This recommendation was considered to be strong although the quality of the evidence it was based on was very low. The Working Group believed this recommendation would be acceptable and feasible to all stakeholders.

IMPLEMENTATION CONSIDERATIONS

The Working Group members considered the recommendations provided above to be the ideal standard of care and would be feasible to implement. Furthermore, they may improve current health inequities by ensuring the same standards of care for all patients no matter where they are treated in Ontario, particularly with respect to access to a medical oncology referral. Unfortunately, the supportive measures required when on adjuvant systemic chemotherapy might highlight inequities in the system as these usually require some out-of-pocket expenses, which may not be affordable to all patients. Overall, there is the potential for better outcomes for patients with resected PDAC across the province. The recommendations would not require a significant change to the current system. The Working Group believed the outcomes valued in this guideline would align well with patient values and patients would view these recommendations as acceptable. Moreover, the Working Group believed that the interpretation of the evidence provided in this guidance document would align with the interpretation of most members of the clinical community.

FURTHER RESEARCH

There is insufficient high-quality evidence regarding the role of radiation or CRT in the context of modern chemotherapy regimens for resected PDAC; further research to define the role for radiation is encouraged. Likewise, further research regarding the role of adjuvant SBRT for resected PDAC is encouraged.

GUIDELINE LIMITATIONS

The literature with respect to the use of adjuvant CRT, particularly in combination with modern chemotherapy regimens, is limited in the setting of resected PDAC. The literature regarding adjuvant SBRT is also currently quite limited in this population.

Role of Adjuvant Treatment in Resected Pancreatic Ductal Adenocarcinoma

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

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

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

JUSTIFICATION FOR GUIDELINE

This guidance document was prompted owing to variations in practice across the province of Ontario and because new data regarding adjuvant treatment are now available.

GUIDELINE DEVELOPERS

This guideline was developed by the Gastrointestinal Disease Site Group (GI DSG) (Appendix 1).

The project was led by a small Working Group of the GI DSG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology, radiation oncology, surgical oncology, and health research methodology. Other members of the GI DSG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all guideline development members are summarized in Appendix 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle (20, 21). This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework (22) as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature

to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Existing guidelines would be included if they were evidence-based guidelines with systematic reviews that addressed at least one of the research questions. Only guidelines based on a systematic review and covering a guideline question were retained. In addition, guidelines older than three years (published before 2018) were excluded and guidelines based on consensus/expert opinion were excluded.

The following sources were searched for guidelines on November 25, 2021: Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology (ASCO), National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia, National Institute for Health and Care Excellence, European Society for Medical Oncology (ESMO), Geneva Foundation for Medical Education and Research, American Society for Radiation Oncology (ASTRO), ECRI database, and Canadian Partnership Against Cancer. No suitable guidelines were found from these sources. MEDLINE and EMBASE were also searched. The search strategy can be found in Appendix 3. A total of 470 documents were uncovered. Of these, 39 underwent full-text review and one was retained (see Figure 1). This guideline contained one recommendation that was considered to be endorsable for Question 3.

Assessment of Guideline(s)

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument (22). The guideline endorsement criterion was that the AGREE II rigour of development domain, which assesses the methodological quality of the guideline, was above 50%.

A guideline search uncovered 832 guidelines of which 43 underwent a full-text review. One guideline by Palta et al. (1) was retained as an appropriate source document for endorsement for Question 3 only. Two reviewers evaluated this guideline independently using the AGREE II tool. The rigour of development domain was 81%, which met the a priori endorsement criterion noted above. All other domains were between 78% and 96% except the applicability domain, which scored 40%. This was mainly owing to this guideline not discussing the potential resource implications of applying their recommendations. Overall, both reviewers recommended this guideline for use (Table 3-1).

Table 3-1: Evaluation of included guideline using AGREE II.

DOMAIN	ITEM	APPRAISER 1	APPRAISER 2	DOMAIN SCORE
Scope and Purpose	1. The overall objective of the guideline is (are) specifically described.	7	6	89%
	2. The health question(s) covered by the guideline is (are) specifically described.	7	7	
	3. The population to whom the guideline is meant to apply is specifically described.	6	5	
Stakeholder Involvement	4. The guideline development group includes individuals from all the relevant professional groups.	7	6	78%
	5. The views and preferences of the target population have been sought.	7	5	
	6. The target users of the guideline are clearly defined.	5	4	
Rigour of Development	7. Systematic methods were used to search for evidence.	6	6	81%
	8. The criteria for selecting the evidence are clearly described.	5	4	
	9. The strengths and limitations of the body of evidence are clearly described.	5	5	
	10. The methods for formulating the recommendation are clearly described.	5	5	
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	6	6	
	12. There is an explicit link between the recommendations and the supporting evidence.	7	7	
	13. The guideline has been externally reviewed by experts prior to its publication.	7	6	
	14. A procedure for update the guideline is provided.	7	7	
Clarity of Presentation	15. The recommendations are specific and unambiguous.	7	7	92%
	16. The different options for management of the condition or health issue are clearly presented.	6	6	
	17. Key recommendations are easily identifiable.	7	6	
Applicability	18. The guideline describes facilitators and barriers to its application.	4	4	40%
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	4	4	
	20. The potential resource implications of applying the recommendations have been considered.	1	1	
	21. The guideline presents monitoring and/or auditing criterial.	4	5	
Editorial Independence	22. The views of the funding body have not influenced the content of the guideline.	7	6	96%
	23. Competing interests of guideline development group members have been recorded and addressed.	7	7	
Overall Guideline Assessment	Rate the overall quality of this guideline.	6	6	
	I would recommend this guideline for use.	Yes	Yes	

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

Patient and Caregiver-Specific Consultation Group

Four patients/survivors/caregivers participated as Consultation Group members for the PDAC Working Group. They reviewed copies of the project plan/draft recommendations and provided feedback on its/their comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration. Overall, the representatives from the patient and caregiver group found the recommendations to be clear and unambiguous and reflected the available evidence. Moreover, they thought that the recommendations addressed issues and outcomes important to patients.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

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- Sara Miller for copy editing.

Role of Adjuvant Treatment in Resected Pancreatic Ductal Adenocarcinoma

Section 4: Systematic Review

INTRODUCTION

Pancreatic cancer is the twelfth most common cancer, accounting for a projected 2.7% of all new incident cases in 2020 in Canada. Despite this low incidence rate, pancreatic cancer is the fourth leading cause of cancer deaths in both men and women. Combining both sexes makes this disease the third leading cause of cancer deaths in Canada at 6.6% based on 2021 projections. Approximately 6700 Canadians (3700 men and 3000 women) will be diagnosed with pancreatic cancer in 2021 and 5600 (2900 men and 2700 women) will die from it (23). Importantly, the projected increase in the incidence of pancreatic cancer over the next 10 years is expected to make pancreatic cancer the second most common cause of death by 2030 (24). Surgery is the pillar of curative treatment for pancreatic cancer, followed by adjuvant chemotherapy (25). Prior to recently published evidence of emerging chemotherapeutic regimens, the standard adjuvant chemotherapy consisted of a six-month course of either a gemcitabine or a 5-FU/leucovorin regimen (9, 15, 26). However, in the setting of recently published evidence of these emerging regimens, the optimal regimen to use has been unclear. Moreover, there remain questions regarding the utility of including adjuvant radiation to adjuvant chemotherapy as well as questions surrounding the use of adjuvant SBRT, which is a newer technology.

The purpose of this guidance document is to synthesize the evidence surrounding the role of adjuvant treatment (chemotherapy, CRT, and SBRT) in resected PDAC as outlined in the research questions below.

This systematic review has been registered on the PROSPERO website (International prospective register of systematic reviews) with the following registration number CRD42020179816 (https://www.crd.york.ac.uk/PROSPERO/#recordDetails).

RESEARCH QUESTION(S)

This guidance document examines the evidence to answer the following questions:

1) What is the role of adjuvant chemotherapy in the treatment of patients with resected PDAC with respect to OS, PFS, toxicity/safety and QOL?

2) What is the role of adjuvant CRT in the treatment of patients with resected PDAC with respect to OS, PFS, toxicity/safety and QOL?

3) What is the role of adjuvant SBRT in the treatment of patients with resected PDAC with respect to OS, PFS, toxicity/safety and QOL?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

- Databases searched: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews
- Years covered: 2016 to November 25, 2021
- Search terms: See Appendix 3
- Selection criteria: English language systematic review that covered any of the current guideline questions with similar inclusion/exclusion criteria that did not have an existing evidence-based guideline to endorse or adapt.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 16-item AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2) (27) tool to determine whether existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base. If more than one systematic review met the inclusion criteria, then one systematic review for each research question was selected by one reviewer (RC) based on its age, quality, and the best match with our study selection criteria stated below.

Search for Primary Literature

For each outcome per research question, if no systematic review was included, then a search for primary literature was conducted. For any included systematic review, an updated search for primary literature was performed from the point in time that the existing systematic review search ended. If any included systematic review was limited in scope, then a search for primary literature to address the limitation in scope was conducted.

Literature Search Strategy

MEDLINE and EMBASE were searched for primary studies beginning from January 2000 if there was no systematic review included for a given question. If a systematic review was included the search for primary studies began from the point that the search timeframe from the included systematic review ended. Please see Appendix 3 for the full search strategy.

Study Selection Criteria and Process

Inclusion Criteria

- English language
- Adults with resected PDAC
- Includes a comparison of interest:
    - Adjuvant chemotherapy versus another adjuvant chemotherapy, adjuvant CRT, or no adjuvant treatment
    - Adjuvant CRT versus another adjuvant CRT, adjuvant chemotherapy alone or no adjuvant treatment
    - Adjuvant SBRT versus no adjuvant SBRT
- Includes at least one outcome of interest: OS, PFS, toxicity/safety, QOL
- RCTs (if available). If RCTs not available other comparative studies will be retained.
- N=30 minimally

Exclusion Criteria

- Case studies, commentaries, editorials

A review of the titles and abstracts was conducted by one reviewer (RC) independently. For studies that warranted full-text review, one reviewer (RC) independently reviewed each study. If uncertainty existed for a given study a second reviewer (JB) would review the paper in question.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by one Working Group member (RC) independently, with all extracted data and information audited subsequently by an independent auditor. Ratios, including hazard ratios, were expressed with a ratio of <1.0 indicating that the outcome was better in the intervention group compared with the control group.

RCTs were assessed for quality and potential bias using the second version of the Cochrane Risk of Bias tool (RoB2) and all non-RCTs, if any were included, were assessed using the Cochrane Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool (https://sites.google.com/site/riskofbiastool/).

Synthesizing the Evidence

Meta-analysis was not planned owing to the use of existing systematic reviews with meta-analysis and existing guidelines.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each research question, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed.

RESULTS

Search for Systematic Reviews

A search for systematic reviews uncovered 1348 documents. Of these, 29 underwent full-text review and three (4, 5, 16) met the pre-planned inclusion criteria (Figure 4-1). These systematic reviews were used for Questions 1 and 2.

Search for Primary Literature

A search for primary literature was conducted for Questions 1 and 2 from the point the searches for the included systematic reviews ended. A search for primary literature for Question 3 was not conducted as a recommendation from an existing guideline was adopted.

Literature Search Results

For the individual study literature search there were 13,575 hits. Of these 64 underwent a full-text review and four were retained; RTOG 0848 (28) as well as the Taiwan Cooperative Oncology Group (TCOG) T3207 trial (29), an update of the APACT trial (30) and an update of the ESPAC-4 trial (31) which were in abstract form. A search for a full publication of the TCOG T3207 trial yielded one other abstract (32). For a summary of the full literature search results (including guidelines and systematic reviews) please refer to Figure 4-1, which is a flow diagram depicting the inclusion and exclusion of all studies identified for this guidance document. A summary of all included studies is reported in Table 4-1.

Figure 4-1. Literature search results flow diagram.

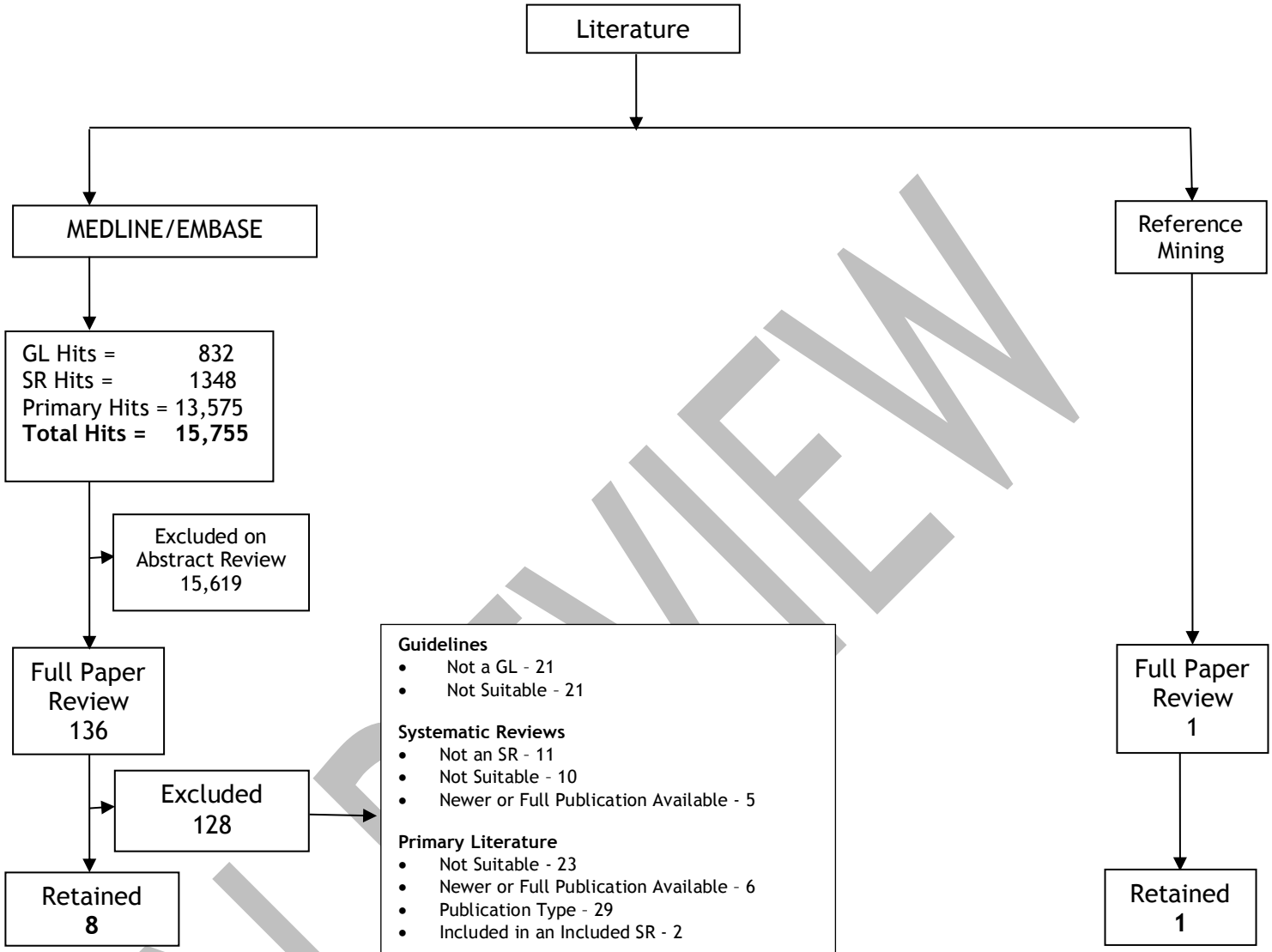

Table 4-1. Studies selected for inclusion

QUESTION	Number of studies (Papers) retained	References
1. What is the role of adjuvant chemotherapy in the treatment of patients with resected PDAC?	5 (5)	3,4,28,30,31
2. What is the role of adjuvant CRT in the treatment of patients with resected PDAC?	2 (3)	15, 29,32
3. What is the role of SBRT in the treatment of those with resected PDAC?	1 (1)	19

Abbreviations: CRT=chemoradiation therapy; PDAC=pancreatic ductal adenocarcinoma; SBRT=stereotactic body radiation therapy

Certainty of the Evidence

Various study designs are included in this guidance document: guideline, systematic reviews and RCTs. The included guideline was evaluated using the AGREE II tool (22) and was deemed to be of sufficient quality to include in the current guidance document (see Section 3). Three systematic reviews were retained and were evaluated using the AMSTAR 2 tool (27) (Table 4-2). RCTs were assessed using the second version of the Cochrane Risk of Bias tool (RoB2) (https://sites.google.com/site/riskofbiastool/) (Table 4-3).

Systematic Reviews

Three systematic reviews were retained and were evaluated using the AMSTAR 2 tool (27). These systematic reviews only included RCTs and overall, they were strong methodologically having scored a 'yes' to most of the items included in this tool. There were only a few items that were scored a 'no' for each study. No study provided a list of excluded studies; however, this is understandable as these lists would have numbered in the thousands. No systematic review provided the sources of funding for the studies included in the reviews. It is unknown if these data were not collected or if they were just not reported for brevity. No systematic review included an evaluation of publication bias. The results in all these systematic reviews suffer from indirectness owing to the differences in chemotherapy regimens used in each of the included studies.

RCTs

Four RCTs presented in five publications (28-32) were included in this guidance document and were assessed using Cochrane's RoB2 (chapter 8) (https://sites.google.com/site/riskofbiastool/) (Table 4-3). The trial by Abrams et al. (28) was assessed to have a low risk of bias in all domains of the RoB2 and therefore had an overall low risk of bias for all outcomes. The TCOG T3207 trial was only reported in abstract form (29, 32). It should be noted that ClinicalTrials.gov was also searched to try and obtain as much information as possible regarding this trial. There was insufficient information about the randomization procedures, deviations from the intended intervention, and selection of reported outcomes to make a good judgement regarding risk of bias. These were, therefore, rated as having some concerns. This unclear risk of bias may simply be a consequence of incomplete reporting but that is unknown. Consequently, the overall risk of bias for this trial was considered to have some concerns. This evaluation could change once these data are fully published and more information regarding its methodology is available. Risk of bias was also assessed for the APACT (30) and ESPAC-4 (31) trials as the updates for these trials were included

in the evidentiary base. Although these two updates were only available in abstract form, information for the purposes of assessing risk of bias was obtained from other trial publications and ClinicalTrials.gov. Both of these trials are open label trials, so the overall risk of bias assessment is assessed as having some concerns because one domain of the RoB2 tool (Measurement of Outcome Bias) is assessed as having some concerns,

Systematic Reviews

Table 4-2. Evaluation of included systematic reviews using AMSTAR2

ITEM	Parmar et al. 2020 (4)	Kamarajah et al. 2020 (5)	Xu et al. 2017 (16)
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Y	Y	Y
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	PY	Y	Y
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Y	Y	Y
4. Did the review authors use a comprehensive literature search strategy?	Y	Y	Y
5. Did the review authors perform study selection in duplicate?	Y	Y	N
6. Did the review authors perform data extraction in duplicate?	Y	N	Y
7. Did the review authors provide a list of excluded studies and justify the exclusions?	N	N	N
8. Did the review authors describe the included studies in adequate detail?	Y	Y	PY
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Y	Y	Y
10. Did the review authors report on the sources of funding for the studies included in the review?	N	N	N
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Y	Y	Y
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Y	Y	Y
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Y	Y	Y
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed I the results of the review?	Y	N	N
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N	N	N
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	N	Y	Y

Abbreviations: N=no; PICO=Population, Intervention, Comparison, Outcome; PY=partial yes; Y=yes

RCTs

Table 4-3. Evaluation of included randomized controlled trials using Cochrane's Risk of Bias tool

Study	Comparison	Randomization Bias	Deviations from the Intended Interventions Bias	Missing Outcome Data Bias	Measurement of Outcome Bias	Reporting Bias	Overall Risk of Bias
Tempero et al. 2021 (30) (APACT update) *abstract*	Nab-P/Gem vs. Gem	Low	Low	Low	Some concerns	Low	Some concerns
Neoptolemos et al. 2020 (31) (ESPAC-4 update) *abstract*	GemCap vs. Gem	Low	Low	Low	Some concerns	Low	Some concerns
Abrams et al. 2020 (28)	Gem vs. Gem/Erlotinib	Low	Low	Low	Low	Low	Low
TCOG T3207, 2018/19(29, 32) *abstract*	Gem vs. Gem/CRT	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns

Abbreviations: CAP=capecitabine; CRT=chemoradiation; Gem=gemcitabine; nab-P=nab-paclitaxel

Outcomes

Question 1: What is the role of adjuvant chemotherapy in the treatment of patients with resected PDAC?

Two systematic reviews with network meta-analyses were retained (4, 5). The Parmar et al. (4) systematic review included phase III trials of adjuvant chemotherapy in resected PDAC. Direct pairwise random effects meta-analysis was conducted where possible. Indirect comparisons were evaluated using network meta-analysis. This systematic review was comprised of 10 publications of 11 important RCTs that included 4920 participants (two RCTs were reported in one paper). Five RCTs compared an adjuvant chemotherapy to observation: CONKO-001(6), JSAP-02 (7), ESPAC-3 (v1) (8), ESPAC-1 Plus (8), and ESPAC-1 (9). Six RCTs compared two different adjuvant chemotherapy regimens: APACT (10), PRODIGE (11), ESPAC-4 (12), CONKO-005 (13), JASPAC-01 (14), and ESPAC-3 (15). In all but one of the trials, 55% to 88% of participants had R0 resections. ESPAC-4 (12) was the lone exception wherein 60% of participants had an R1 resection.

Results of direct pairwise meta-analysis comparing adjuvant chemotherapy with observation demonstrated significantly better overall DFS (HR, 0.56; 95% CI, 0.46 to 0.68; p<0.00001) with adjuvant chemotherapy. Likewise, direct pairwise meta-analysis comparing other adjuvant chemotherapy regimens with gemcitabine alone also demonstrated significantly better DFS (HR, 0.76; 95% CI, 0.63 to 0.92, p=0.005) for other adjuvant chemotherapy. Indirect comparisons using network meta-analysis demonstrated that DFS was significantly improved with mFOLFIRINOX compared with 5-FU (HR, 0.56; 95% CI, 0.43 to 0.73), gemcitabine (HR, 0.58; 95% CI, 0.46 to 0.73), gemcitabine plus capecitabine (HR, 0.67; 95% CI, 0.51 to 0.90), gemcitabine plus erlotinib (HR, 0.62; 95% CI, 0.453 to 0.84) and gemcitabine plus nab-paclitaxel (HR, 0.66; 95% CI, 0.49 to 0.89). Similar improvements in DFS were also reported with S-1 compared with 5-FU, gemcitabine, gemcitabine plus capecitabine, gemcitabine plus erlotinib, and gemcitabine plus nab-paclitaxel (4).

Results of direct pairwise meta-analysis comparing adjuvant chemotherapy with observation demonstrated significantly better OS (HR, 0.73; 95% CI, 0.63 to 0.84; p<0.00001) with adjuvant chemotherapy. Similarly, direct pairwise meta-analysis comparing other adjuvant chemotherapy regimens with gemcitabine alone also demonstrated significantly better OS (HR, 0.72; 95% CI, 0.61 to 0.86, p=0.0002) for other adjuvant chemotherapy. Indirect comparisons using network meta-analysis demonstrated that OS was significantly improved with mFOLFIRINOX compared with 5-FU (HR, 0.64; 95% CI, 0.46 to 0.90), gemcitabine (HR, 0.64; 95% CI, 0.47 to 0.87) and gemcitabine plus erlotinib (HR, 0.68; 95% CI, 0.47 to 1.00) but not gemcitabine plus capecitabine (HR, 0.78; 95% CI, 0.54 to 1.12) or gemcitabine plus nab-paclitaxel (HR, 0.78; 95% CI, 0.54 to 1.13). Likewise, indirect comparisons using network meta-analysis demonstrated that OS was significantly improved with S-1 compared with 5-FU, gemcitabine, gemcitabine plus capecitabine and gemcitabine plus erlotinib, and gemcitabine plus nab-paclitaxel (4).

Updated OS results for APACT (30) and ESPAC-4 (31) are similar to the results initially reported for these trials that were included in the Parmar et al. (4) network meta-analysis.

Results of direct pairwise comparisons of grade 3/4 hematological toxicities demonstrate no significant differences between other adjuvant chemotherapy and gemcitabine with respect to thrombocytopenia (HR, 0.64; 95% CI, 0.27 to 1.50; p=0.30), neutropenia (HR, 0.85; 95% CI, 0.55 to 1.32; p=0.48), and febrile neutropenia (HR, 1.27, 95% CI, 0.48 to 3.38; p=0.63). However, anemia was significantly improved with other adjuvant chemotherapy compared with gemcitabine alone (HR, 0.74; 95% CI, 0.59 to 0.94; p=0.01) (4). No QOL data were reported (4).

The Kamarajah et al. (5) network meta-analysis was very similar to the Parmar et al. (4) network meta-analysis covering almost the exact same time frame. The same conclusion, that the optimal adjuvant chemotherapy following resection for PDAC is S-1 or mFOLFIRINOX, was reported.

A search for primary studies from the point that the Parmar et al. (4) systematic review ended yielded one publication of a randomized phase II trial comparing gemcitabine to gemcitabine plus erlotinib in those with resected head of pancreas adenocarcinoma (28). Median OS for gemcitabine plus erlotinib versus gemcitabine was 28.1 months versus 29.9 months (HR, 1.04; 95% CI, 0.79 to 1.38; p=0.62 [one-sided, log-rank]). Moreover, there was no DFS advantage to the combination chemotherapy regimen compared with the gemcitabine monotherapy (HR, 1.02; 95% CI, 0.80 to 1.31; p=0.58 [one-sided, log-rank]).

The positive results from Japanese JASPAC-01 (14) were included in both the Kamarajah et al. (5) and Parmar et al. (4) analyses. However, the applicability to European and North American patients has not been established. Pharmacokinetics and pharmacodynamics of S-1 differences may account for the increased toxicities in the latter populations. We have therefore not included studies that used S-1 in our analysis or recommendation development.

Question 2: What is the role of adjuvant CRT in the treatment of patients with resected PDAC?

One systematic review with network meta-analysis was retained (16). The Xu et al. (16) study was designed to determine the optimal adjuvant chemotherapy for resected pancreatic adenocarcinoma. A total of 13 RCTs that included 4098 participants were included in the network meta-analysis; however, for the purposes of the current guideline only the trial data dealing with CRT were considered: Regine et al. (17), EORTC 40891 (18), ESPAC-1 (9), and Kalser et al. (19). There was no significant difference between fluorouracil and fluorouracil plus CRT with respect to one-year survival (HR, 1.07; 95% CI, 0.44 to 2.53), three-year survival (HR, 1.28; 95% CI, 0.64 to 2.46) and five-year survival (HR, 1.88; 95% CI, 0.60 to 7.02). Likewise, there was no significant difference between gemcitabine and gemcitabine plus CRT with respect to one-year survival (HR, 0.86; 95% CI, 0.20 to 3.59), three-year survival (HR, 0.93; 95% CI, 0.33 to 2.57) and five-year survival (HR, 1.77; 95% CI, 0.30 to 11.98). Although gemcitabine plus CRT resulted in more toxicity than gemcitabine alone, the difference was not statistically significant (HR, 0.70; 95% CI, 0.00 to 537.3). No QOL data were reported.

A search for primary studies from the point that the Xu et al. (15) systematic review ended yielded two abstracts of one RCT (29, 32). The TCOG T3207 trial (147 participants) compared adjuvant gemcitabine with adjuvant gemcitabine plus CRT. Although the 2019 ESMO abstract was the more recent publication, the 2018 ESMO abstract contained much more information; therefore, it was also included. The primary endpoint was recurrence-free survival (RFS). There was no significant difference in median RFS in the two arms of this trial (12.1 months vs. 13.3 months; HR, 0.96; 95% CI, 0.67 to 1.37; p=0.80) or in OS (23.5 months vs. 21.5 months; HR, 1.07, 95% CI, 0.74 to 1.55; p=0.73). Moreover, grade 3/4 toxicity was similar in the two arms (66% vs. 73%, p=0.34).

Question 3: What is the role of adjuvant SBRT in the treatment of patients with resected PDAC?

One guideline produced by ASTRO (1) was retained from the guideline search as it sufficiently addressed the issue of SBRT following resection of PDAC and was therefore endorsed by the Working Group. Only the recommendation pertaining to adjuvant SBRT is being endorsed (see page 326 of the Palta et al. guideline). The authors of this guideline conducted a systematic review and recommend that adjuvant SBRT only be used within a clinical trial or multi-institutional registry. This recommendation was considered to be strong although the quality of the evidence it was based on was very low. All members of the ASTRO guideline Working Group agreed with this recommendation.

Ongoing, Unpublished, or Incomplete Studies

Gemcitabine Hydrochloride with or without Erlotinib Hydrochloride Followed by the Same Chemotherapy Regimen with or without Radiation Therapy and Capecitabine or Fluorouracil in Treating Patients with Pancreatic Cancer that has been Removed by Surgery	
Protocol ID:	NCT01013649
Date last modified:	June 23, 2021
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	Overall survival
Accrual:	545 will be accrued
Sponsorship:	National Cancer Institute
Status:	Active, not recruiting

Trial Comparing Adjuvant Chemotherapy with Gemcitabine versus mFolfirinox to Treat Resected Pancreatic Adenocarcinoma	
Protocol ID:	NCT01526135
Date last modified:	February 16, 2021
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	Disease free survival
Accrual:	493 have been accrued
Sponsorship:	UNICANCER
Status:	Active, not recruiting

DISCUSSION

In the past decade, several landmark randomized trials have advanced the adjuvant chemotherapy standard for patients with resected pancreatic cancer and informed the role of radiation when combined with chemotherapy.

Comparative adjuvant chemotherapy trials have led to a shift from single-agent chemotherapy to more effective combination regimens. Gemcitabine monotherapy has been the control arm of choice in the several large-scale randomized trials reported. The PRODIGE (11) and ESPAC-4 (12) trials with experimental arms of mFOLFIRINOX and gemcitabine plus capecitabine, respectively, met their study endpoints and have been adopted as new standards. Unfortunately, the APACT trial (10) of gemcitabine plus nab-paclitaxel was interpreted as a negative study, despite the regimen's established role in the first-line metastatic setting.

The recommendations in Question 1 stating a preference in favour of the mFOLFIRINOX regimen versus the gemcitabine plus capecitabine or gemcitabine-alone regimens is based on the comparative survival advantage derived in the network meta-analysis (4). An important qualification here is that there is a lack of direct comparative data for efficacy or toxicities. Additionally, important patient characteristics including R1 resection, nodal status, and baseline CA19-9 varied considerably among the trials. Thus, it is important at a practical level that patient characteristics, perhaps the most important being functional status, will influence the choice of adjuvant regimen when the discussion between caregiver and patient takes place.

The role for radiation in the adjuvant setting continues to be debated. Trials comparing a radiation plus chemotherapy (CRT) strategy to modern chemotherapy regimens are lacking. ESPAC-1 trial showed no survival difference among 175 patients who received postoperative CRT when compared to the 178 who did not (median overall survival 15.5 versus 16.1 months, respectively) (33). In the subsequent intent-to-treat analysis of the 289 patients, there was a trend toward worse survival for the group receiving CRT (9). A meta-analysis of nine randomized trials comparing six different adjuvant strategies reflected a lack of precision and it is difficult to draw any meaningful conclusions in terms of benefit of CRT (34). The EORTC 40013 phase II study randomly assigned 90 patients with resected pancreatic cancer (70% node positive) to two cycles of weekly gemcitabine alone followed by radiation therapy 5040 cGy in 28 daily fractions of 180 cGy. Initially, the control group was observation alone (n=4), but the protocol was amended, and the remainder of the control group (n=41) received four cycles of gemcitabine alone. The median overall survival was 24 months in both arms and the DFS was 12 months versus 11 months in the control group. The rate of local recurrence in the CRT group was lower (11% vs. 24%) but the rates of distant progression were similar (40% vs. 42%) (35). Additional information from NRG/RTOG 0848 on the role of CRT is awaited (28). Based on above data, many clinicians do not recommend concomitant CRT after resection of pancreatic cancer. However, some find adjuvant CRT is a reasonable approach for patients who have high-risk features such as a positive margin (R1 resection) or node-positive disease and when FOLFIRINOX was not received. Evidence for this approach remains limited to subgroup analyses of larger trials. The conclusions in this guideline are consistent with statements from other specialty organizations including ASCO (36) and ESMO (37).

An important trial comparing the fluoropyrimidine analogue S-1 to gemcitabine in the adjuvant setting demonstrated positive results in a Japanese population (14). However, the applicability to European and North American patients has not been established. Pharmacokinetics and pharmacodynamics of S-1 differences may account for the increased toxicities in the latter populations. We have therefore not included studies that used S-1 in our analysis or recommendation development.

Among the varied areas of active clinical research in resectable PDAC, there are two current research priorities we wish to highlight. The neo-adjuvant setting is receiving a great deal of attention, represented for instance by the US-led ALLIANCE A021806 and Dutch

PREOPANC-3 trials. Patients with pancreatic cancer who have underlying germline mutations represent specific populations for which novel therapeutic approaches are under active investigation. Emerging evidence of agents that target such mutations, for example poly adenosine diphosphate-ribose polymerase (PARP) inhibition for DNA damage repair mutations, may provide future options for patients in the adjuvant setting.

CONCLUSIONS

Adjuvant chemotherapy is recommended for patients with R0 or R1 resected PDAC. The recommended regimen is mFOLFIRINOX with alternative options of gemcitabine plus capecitabine or gemcitabine alone. There is insufficient evidence to recommend the use of adjuvant CRT in this population and adjuvant SBRT should only be used within a clinical trial or multi-institutional registry.

Role of Adjuvant Treatment in Resected Pancreatic Ductal Adenocarcinoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the five members of the GDG Expert Panel, five members voted, and none abstained, for a total of 100% response in December 2021. Of those who voted, five approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. In Recommendation 1 please be more specific with respect to what 'appropriate' patients means.	We have clarified the wording.
2. Moving some statements from Key Evidence to Qualifying Statements or from Qualifying Statements to Key Evidence.	We have moved some of the statements.
3. Include the patient representative comments.	We have included the patient and caregiver representative comments.
4. Make Recommendation 2 more specific.	We have made modifications to the wording to be more specific
5. Add outcomes of interest to the guideline questions.	We have made this change.
6. Add in HRs of indirect comparisons from network meta-analysis.	We have added in the HRs.
7. Add in toxicity data.	We have added this in.
8. In Recommendation 2 clarify that a discussion regarding radiation therapy is reasonable when there are positive margins and/or positive nodes.	The qualifying statement for Recommendation 2 has been amended to reflect this.

RAP Review and Approval

Three RAP members reviewed this document in December 2021. One RAP member approved the document, and two RAP members conditionally approved the document. This meant that they approved the document if some of their suggested changes were made (which they were). The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. In the guideline objectives, the term 'adjuvant treatment' should be expanded to clarify the specific treatment.	We have clarified and been specific as to what is meant by adjuvant treatment.
2. Add some information into the introduction regarding what has been the standard of care in adjuvant treatment for resected PDAC.	We have added this information in.
3. How do you know that the systematic reviews contain all the relevant studies?	We only use systematic reviews that use good-quality methods for this very reason. We then search for any additional studies that might have been published since the end date of the included systematic review.
4. Add in a limitations section.	We added in a limitations section.
5. How is the evidence used to make recommendations?	This is covered in Section 3 as well as the justification for each recommendation in Section 2.
6. Add in toxicity data.	We added in the toxicity data.
7. Should 'borderline resectable' be defined in the Target Population section.	This section was reworded to clarify that the target population covers those with 'resected' PDAC
8. Add in the QOL data.	QOL data were not reported in the included evidence, and this has now been explicitly noted in this guidance document.
9. Should the recommendations for CRT and SBRT be different?	There are differing amounts of evidence for CRT and SBRT in this population. Specifically, there is much more evidence regarding CRT than SBRT, which is reflected in the differing recommendations.

Patient and Caregiver-Specific Consultation Group

Four patients/survivors/caregivers participated as Consultation Group members for the Working Group. They reviewed the draft recommendations and provided feedback on its comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The main comments from the Consultation Group are summarized in Table 5-3.

Table 5-3. Summary of the Working Group's responses to comments from the Consultation Group.

Comments	Responses
1. The recommendations are clear and unambiguous.	No changes made.
2. The recommendations consider issues and outcomes that are important to patients.	No changes made.
3. The recommendations reflect the evidence, but the toxicity data need to be added in.	We have added the toxicity data.

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Three targeted peer reviewers from Ontario and Ireland who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Three agreed to be the reviewers (Appendix 1). Three responses were received. Results of the feedback survey are summarized in Table 5-3. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.					3
2. Rate the guideline presentation.				1	2
3. Rate the guideline recommendations.				1	2
4. Rate the completeness of reporting.				2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				2	1
6. Rate the overall quality of the guideline report.				1	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.					3
8. I would recommend this guideline for use in practice.					3
9. What are the barriers or enablers to the implementation of this guideline report?	• No specific implementation barriers identified.				

Table 5-4. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	Responses
1. A comment that treatment-related costs are not specified.	PEBC guidelines never include cost analyses. There are groups with this specific expertise.
2. A comment that the placement of the T3207 trial should be in Question 2 as it focuses on CRT.	We have made this change.
3. A comment that R1 disease should be directly addressed	We have added in information regarding node positive and R1 disease in information provided for Recommendation 2.
4. A comment about the inclusion of trials using S-1.	We have clarified that although JASPAC-01 was included in the included systematic reviews, its applicability to European and North American patients has not been established. Therefore, S-1 was not included in our analysis and no recommendations were made regarding S-1.

5. A comment regarding potential inequities in patients receiving mFOLFIRINOX.	We have clarified this section.
6.A comment to add some information regarding neoadjuvant chemotherapy into the discussion.	We have added a paragraph to the discussion.
7.A comment that some of the trials included in the guideline and systematic review did not use standard fractionation for radiation and that trials are ongoing.	We have added some information to the discussion.
8.A few editorial comments.	We have corrected these.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All medical, radiation and surgical oncologist in the PEBC database were contacted by email to inform them of the survey. A total of 109 oncologists were contacted all of whom practice in Ontario. Six (5.5%) responses were received. Eight stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from six people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1 (17)	1 (17)	4 (67)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1 (17)	2 (33)	3 (50)
3. I would recommend this guideline for use in practice.			1 (17)	1 (17)	4 (67)
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers: • Potential costs to patients of some treatments as identified in the guideline. • Unwillingness of some radiation oncologists to accept that the role of adjuvant radiation is not established through RCTs. • Unwillingness of some radiation oncologists to use adjuvant SBRT in the context of multi-institutional registries where clinical trial is not available. Enablers: • Wide acceptance of potential benefits of available chemotherapy agents.				

Table 5-6. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
1. A comment that some centres with high volumes of patients have considerable expertise in SBRT and therefore perhaps Recommendation 3 should be worded as "formal registries" rather than "multi-institutional registries".	Whereas the Working Group agrees that some centres have considerable expertise in SBRT, Recommendation 3 was not changed as it was adopted directly from a well conducted existing ASTRO guideline.
2. A comment the unwillingness of some radiation oncologists to accept that the role of adjuvant radiation is not established.	This is the reason that the guideline was developed; there will not be 100% agreement on the role of adjuvant radiation, thus, evidence-based guidance is needed.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

References

1. Palta M, Godfrey D, Goodman KA, Hoffe S, Dawson LA, Dessert D, et al. Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2019;9(5):322-32.
2. Valle JW, Palmer D, Jackson R, Cox T, Neoptolemos JP, Ghaneh P, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol. 2014;32(6):504-12.
3. Jones RP, Psarelli EE, Jackson R, Ghaneh P, Halloran CM, Palmer DH, et al. Patterns of recurrence after resection of pancreatic ductal adenocarcinoma: a secondary analysis of the ESPAC-4 randomized adjuvant chemotherapy trial. JAMA Surg. 2019;154(11):1038-48.
4. Parmar A, Chaves-Porras J, Saluja R, Perry K, Rahmadian AP, Santos SD, et al. Adjuvant treatment for resected pancreatic adenocarcinoma: A systematic review and network meta-analysis. Crit Rev Oncol Hematol. 2020;145:102817.
5. Kamarajah SK, Bundred JR, Alrawashdeh W, Manas D, White SA. A systematic review and network meta-analysis of phase III randomised controlled trials for adjuvant therapy following resection of pancreatic ductal adenocarcinoma (PDAC). HPB. 2020;22(5):649-59.
6. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(14):1473-81.
7. Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer. 2009;101(6):908-15.
8. Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer. 2009;100(2):246-50.
9. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350(12):1200-10.
10. Tempero MA, Reni M, Riess H, Pelzer U, O'Reilly EM, Winter JM, et al. APACT: Phase III, multicenter, international, openlabel, randomized trial of adjuvant nabpaclitaxel plus gemcitabine (nab-P/ G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma. J Clin Oncol Conf. 2019;37(Supplement 15).
11. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379(25):2395-406.
12. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011-24.
13. Sinn M, Bahra M, Liersch T, Gellert K, Messmann H, Bechstein W, et al. CONKO-005: Adjuvant chemotherapy with gemcitabine plus erlotinib versus gemcitabine alone in patients after r0 resection of pancreatic cancer: A multicenter randomized phase III trial. J Clin Oncol. 2017;35(29):3330-7.
14. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016;388(10041):248-57.

15. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304(10):1073-81.
16. Xu JB, Jiang B, Chen Y, Qi FZ, Zhang JH, Yuan H. Optimal adjuvant chemotherapy for resected pancreatic adenocarcinoma: A systematic review and network meta-analysis. Oncotarget. 2017;8(46):81419-29.
17. Regine WF, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011;18(5):1319-26.
18. Smeenk HG, van Eijck CH, Hop WC, Erdmann J, Tran KC, Debois M, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Ann Surg. 2007;246(5):734-40.
19. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985;120(8):899-903.
20. Browman GP, Levine MN, Mohide EA, Hayward RS, 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(2):502-12.
21. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the Practice Guidelines Development Cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.
22. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-42.
23. Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, Statistics Canada and the Public Health Agency of Canada. *Canadian Cancer Statistics 2021*. Toronto, ON: Canadian Cancer Society; 2021.
24. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913-21.
25. Canadian Cancer Society's Advisory Committee on Cancer Statistics. *Canadian Cancer Statistics 2017*. Toronto, ON: Canadian Cancer Society; 2017.
26. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297(3):267-77.
27. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
28. Abrams RA, Winter KA, Safran H, Goodman KA, Regine WF, Berger AC, et al. Results of the NRG Oncology/RTOG 0848 adjuvant chemotherapy question-erlotinib+gemcitabine for resected cancer of the pancreatic head: A phase II randomized clinical trial. Am J Clin Oncol. 2020;43(3):173-9.
29. Chen LT. Chemo-radiotherapy in adjuvant therapy of curatively resected pancreatic cancer: Lesions from TCOG T3207 Study. Ann Oncol. 2019;30 (Supplement 6):vi75.
30. Tempero M, O'Reilly E, Van Cutsem E, Berlin J, Philip P, Goldstein D, et al. Phase 3 APACT trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P + Gem) vs gemcitabine (Gem) alone in patients with resected pancreatic cancer (PC): Updated 5-year overall survival. Ann Oncol. 2021;32(Supplement 3):S226.

31. Neoptolemos JP, Palmer DH, Ghaneh P, Valle JW, Cunningham D, Wadsley J, et al. ESPAC-4: A multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP) versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma: Five year follow-up. J Clin Oncol Conf. 2020;38(15).
32. Chang HJ, Chiu YF, Chen JS, Li CP, Ho CL, Shyr YM, et al. Randomized, phase III trial comparing adjuvant gemcitabine (Gem) versus Gem plus chemoradiation (CCRT) in curatively resected pancreatic ductal adenocarcinoma (PDAC): A Taiwan cooperative oncology group study. Ann Oncol. 2018;29 (Supplement 8):viii210.
33. Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet. 2001;358(9293):1576-85.
34. Liao WC, Chien KL, Lin YL, Wu MS, Lin JT, Wang HP, et al. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. Lancet Oncol. 2013;14(11):1095-103.
35. Van Laethem JL, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. J Clin Oncol. 2010;28(29):4450-6.
36. Khorana AA, McKernin SE, Berlin J, Hong TS, Maitra A, Moravek C, et al. Potentially curable pancreatic adenocarcinoma: ASCO clinical practice guideline update. J Clin Oncol. 2019;37(23):2082-8.
37. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v56-68.

Appendix 1. Conflict of Interest Declarations of Members of the PDAC Working Group, Expert Panel, Report Approval Panel, Target Reviewers and Patient Consultation Group.

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors (Working Group), PDAC Expert Panel members, internal and external reviewers and patient consultation group were asked to disclose potential conflicts of interest.

Members of the PDAC Working Group

Name	Specialty	Affiliation	Declarations of interest
Jim Biagi Chair	MO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest.
Mala Bahl	MO	Trillium Health Partners Mississauga, ON	Declared they had no conflicts of interest.
Tarek Elfiki	MO	Windsor Regional Cancer Centre Windsor, ON	Declared they had no conflicts of interest.
Rachel Goodwin	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Received $500 or more in a single year to act in a consulting capacity for Ipsen, Eiasi, Merck, Pfizer, Taiho, AAA, BMS, Apobiologix and Amgen. Received research support from Ipsen, Apobiologix and Pfizer.
Julie Hallet	SO	Odette Cancer Centre Toronto, ON	Received $500 or more in a single year for speaking honoraria from Ipsen, AAA, Medtronic.
Khalid Hirmiz	RO	Windsor Regional Cancer Centre Windsor, ON	Declared they had no conflicts of interest.
Aamer Mahmud	RO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest.
Roxanne Cosby	HRM	Program in Evidence-Based Care McMaster University Hamilton, Ontario	Declared they had no conflicts of interest.

Abbreviations: HRM=health research methodologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Members of the PDAC Expert Panel

Name	Specialty	Affiliation	Declarations of interest
Joseph Del Paggio	MO	Thunder Bay Regional Health Sciences Centre	Spouse has received $500 or more in a single year to act in a consulting capacity as an Infusion Services Provincial Medical Lead Ontario for McKesson.
Kristopher Dennis	RO	Ottawa Hospital Cancer Centre	Declared they had no conflicts of interest.
Shiva Jayaraman	SO	St. Joseph's Health Centre, Toronto	Declared they had no conflicts of interest.
John Lenehan	MO	London Regional Cancer Program	Received $500 or more in a single year for an observership in melanoma for Merck.
Raimond Wong	RO	Juravinski Cancer Centre	Declared they had no conflicts of interest.

Abbreviations: MO=medical oncologist; PDAC=pancreatic ductal adenocarcinoma; RO=radiation oncologist; SO=surgical oncologist

Members of the PDAC Report Approval Panel

Name	Specialty	Affiliation	Declarations of interest
Michelle Ghert	SO	Juravinski Cancer Centre	Declared they had no conflicts of interest.
Donna Maziak	SO	The Ottawa Hospital	Declared they had no conflicts of interest.
Jonathan Sussman	RO	Juravinski Cancer Centre	Declared they had no conflicts of interest.

Abbreviations: RO=radiation oncologist; SO=surgical oncologist

Members of the PDAC Targeted Peer Reviewers

Name	Specialty	Affiliation	Declarations of interest
Kimberley Bertens	SO	The Ottawa Hospital	Received a one-time payment of $1000 for acting as a consultant relating to hepatocellular carcinoma.
Sylvia Ng	RO	Odette Cancer Centre	Is the first author of a published book chapter on the subject matter: Ng SSW, Koong AC, Dawson LA & Coburn NS. Neoadjuvant and adjuvant radiotherapy in operable pancreatic cancer. In: Soreide K & Stattner S, editors. Textbook of pancreatic cancer: principles and practice in surgical oncology. Cham, Switzerland: Springer; 2021, p. 713-728.
Grainne O'Kane	MO	Trinity St. James' Cancer Institute, Dublin, Ireland	Received $500 or more in a single year to act in a consulting capacity for AstraZeneca, Roche, Eisai, Incyte and honoraria from AstraZeneca, Roche and Eisai.

Abbreviations: MO=medical oncologist; PDAC=pancreatic ductal adenocarcinoma; RO=radiation oncologist; SO=surgical oncologist

Members of the PDAC Patient and Caregiver Consultation Group

Name	Declarations of interest
Lise Craig	Declared they had no conflicts of interest.
Lauri Petz	Declared they had no conflicts of interest.
Pat Sevean	Declared they had no conflicts of interest.
Bob Tuck	Declared they had no conflicts of interest.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy.

Appendix 2. Affiliations of the Gastrointestinal Disease Site Group

Name	Specialty	Affiliation
Asma Ali	MO	Ramsey Lake Health Centre Health Sciences North Sudbury, ON
Tim Asmis	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Robert Beecroft	IR	Mount Sinai Hospital Toronto, ON
Scott Berry	MO	Odette Cancer Centre Toronto, ON
Jim Biagi	MO	Cancer Centre of Southeastern Ontario Kingston, ON
Sami Chadi	SO	Toronto Western Hospital Toronto, ON
Kelvin Chan	MO	Odette Cancer Centre Toronto, ON
Charles Cho	RO	Stronach Regional Cancer Program Newmarket, ON
Joseph Del Paggio	MO	Thunder Bay Regional Health Sciences Centre Thunder Bay, ON
Kristopher Dennis	RO	Ottawa Hospital Cancer Centre Ottawa, ON
Tarek Elfiki	MO	Windsor Regional Cancer Centre Windsor, ON
Elena Elimova	MO	Princess Margaret Hospital Toronto, ON
Valerie Francescutti	SO	Hamilton General Hospital Hamilton, ON
Rachel Goodwin	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Robert Gryfe	SO	Mt. Sinai Hospital Toronto, ON
Julie Hallet	SO	Odette Cancer Centre Toronto, ON
Nazik Hammad	MO	Cancer Centre of Southeastern Ontario Kingston, ON
Khalid Hirmiz	RO	Windsor Regional Cancer Centre Windsor, ON
Raymond Jang	MO	Princess Margaret Hospital Toronto, ON
Shiva Jayaraman	SO	St. Joseph's Health Centre Toronto, ON
Derek Jonker	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Maria Kalyvas	RO	Cancer Centre of Southeastern Ontario Kingston, ON

Paul Karanicolas	SO	Odette Cancer Centre Toronto, ON
Erin Kennedy	SO	Mt. Sinai Hospital Toronto, ON
John Lenehan	MO	London Regional Cancer Program London, ON
Aamer Mahmud	RO	Cancer Centre of Southeastern Ontario Kingston, ON
Richard Malthaner	SO	London Regional Cancer Program London, ON
Brandon Meyers	MO	Juravinski Cancer Centre Hamilton, ON
Fayez Quereshy	SO	Princess Margaret Hospital Toronto Western Hospital Toronto, ON
Mark Rother	MO	Peel Regional Cancer Centre Mississauga, ON
Lara Williams	SO	Ottawa Hospital Cancer Centre Ottawa, ON
Raimond Wong	RO	Juravinski Cancer Centre Hamilton, ON
Rebecca Wong	RO	Princess Margaret Hospital Toronto, ON
Kevin Zbuk	MO	Juravinski Cancer Centre Hamilton, ON
Roxanne Cosby	HRM	Program in Evidence-Based Care McMaster University Hamilton, ON

Abbreviations: HRM=health research methodologist; IR=interventional radiologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Appendix 3: Literature Search Strategy for Clinical Practice Guidelines, Systematic Reviews and Primary Literature

Clinical Practice Guidelines

MEDLINE

1 exp Pancreatic Neoplasms/
2 exp Carcinoma, Pancreatic Ductal/ or pancreatic ductal adenocarcinoma.mp.
3 1 or 2
4 exp Evidence-Based Practice/
5 guideline.pt.
6 exp Guideline/ or exp Practice Guideline/
7 practice parameter$.tw.
8 practice guideline$.mp.
9 (guideline: or recommend: or consensus or standards).ti.
10 (guideline: or recommend: or consensus or standards).kw.
11 or/4-10
12 3 and 11
13 limit 12 to yr="2016 -Current"
14 limit 13 to english language

EMBASE

1 pancreatic cancer.mp. or exp pancreas cancer/
2 pancreatic ductal adenocarcinoma.mp.
3 1 or 2
4 adjuvant treatment.mp. or exp adjuvant therapy/
5 exp adjuvant therapy/ or exp cancer adjuvant therapy/
6 4 or 5
7 3 and 6
8 exp evidence based practice/
9 exp practice guideline/
10 practice parameter$.tw.
11 practice guideline$.mp.
12 (guideline: or recommend: or consensus or standards).ti.
13 (guideline: or recommend: or consensus or standards).kw.
14 or/8-13
15 7 and 14
16 limit 15 to yr="2016 -Current"
17 limit 16 to english language

Systematic Reviews

MEDLINE

1	exp Carcinoma, Pancreatic Ductal/ or exp Pancreatic Neoplasms/ or pancreatic ductal adenocarcinoma.mp.
2	exp Meta-Analysis as Topic/
3	meta-analysis.pt.
4	(systematic adj (review: or overview:)).mp.
5	(meta-analy: or metaanaly: or meta analy:).mp.
6	(pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
7	(exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
8	(cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or cancerlit or pubmed or pub-med or medline or med-line).ab.
9	(reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
10	or/2-9
11	(selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
12	(stud: adj1 select:).ab.
13	(11 or 12) and review.pt.
14	10 or 13
15	1 and 14
16	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
17	15 not 16
18	limit 17 to english language
19	limit 18 to yr="2016 - 2020"

EMBASE

1	pancreatic ductal adenocarcinoma.mp. or exp pancreas adenocarcinoma/
2	pancreatic cancer.mp. or exp pancreas cancer/
3	1 or 2
4	adjuvant treatment.mp. or exp adjuvant therapy/
5	exp cancer adjuvant therapy/
6	4 or 5
7	3 and 6
8	exp meta analysis/
9	exp "meta analysis (topic)"/
10	exp "systematic review"/
11	exp "systematic review (topic)"/
12	(meta analy$ or metaanaly$ or meta-analy$).tw.
13	(systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.

14 (systematic adj (review: or overview:)).tw.
15 exp "review"/
16 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or cancerlit or pubmed or pub-med or medline or med-line).ab.
17 (reference list$ or bibliograph$ or hand-search$ or relevant journal$ or manual search$).ab.
18 or/8-17
19 (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
20 (study adj selection).ab.
21 (19 or 20) and review.pt.
22 18 or 21
23 7 and 22
24 (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
25 23 not 24
26 limit 25 to english language
27 limit 26 to yr="2016 - 2020"

Primary Individual Studies – Chemotherapy

MEDLINE

1	exp Carcinoma, Pancreatic Ductal/ or exp Pancreatic Neoplasms/ or pancreatic ductal adenocarcinoma.mp.
2	resected pancreatic ductal adenocarcinoma.mp.
3	1 or 2
4	exp Chemotherapy, Adjuvant/
5	exp Antineoplastic Agents/
6	exp Drug Therapy/
7	4 or 5 or 6
8	3 and 7
9	limit 8 to yr="2019 - 2020"
10	limit 9 to english language
11	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
12	10 not 11

EMBASE

1	pancreatic ductal adenocarcinoma.mp. or exp pancreas adenocarcinoma/
2	exp pancreas carcinoma/
3	exp pancreas tumor/
4	1 or 2 or 3
5	exp adjuvant chemotherapy/
6	exp antineoplastic agent/
7	exp drug therapy/
8	5 or 6 or 7
9	4 and 8
10	limit 9 to yr="2019 - 2020"
11	limit 10 to english language
12	(editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
13	11 not 12

Primary Individual Studies – CRT

MEDLINE

1 exp Carcinoma, Pancreatic Ductal/ or exp Pancreatic Neoplasms/ or pancreatic ductal adenocarcinoma.mp.
2 resected pancreatic ductal adenocarcinoma.mp.
3 1 or 2
4 exp Chemoradiotherapy, Adjuvant/
5 3 and 4
6 limit 5 to yr="2016 - 2020"
7 limit 6 to english language
8 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
9 7 not 8

EMBASE

1 pancreatic ductal adenocarcinoma.mp. or exp pancreas adenocarcinoma/
2 exp pancreas carcinoma/
3 exp pancreas tumor/
4 1 or 2 or 3
5 exp adjuvant chemoradiotherapy/
6 4 and 5
7 limit 6 to yr="2016 - 2020"
8 limit 7 to english language
9 (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
10 8 not 9