

# Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Pancreatic Adenocarcinoma

The Singapore Cancer Network (SCAN) Pancreatic Cancer Workgroup

## Abstract

**Introduction:** The SCAN pancreatic cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for systemic therapy for pancreatic adenocarcinoma in Singapore. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Cancer Comprehensive Network (2014), the European Society of Medical Oncology (2012), Cancer Care Ontario (2013), the Japan Pancreas Society (2013) and the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, and the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (2005). Recommendations on the management of resected, borderline resectable, locally advanced and metastatic pancreatic adenocarcinoma were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines for systemic therapy for pancreatic adenocarcinoma in Singapore.

Ann Acad Med Singapore 2015;44:388-96

**Key words:** Singapore context, Treatment recommendation

## Introduction

Worldwide, pancreatic cancer is the thirteenth most common adult malignancy and the seventh most common cause of cancer death. In Singapore, it is the eleventh and twelfth most common cancer among Singaporean men and women respectively. Although pancreatic cancer did not feature among the 10 most common cancers in Singapore, it represented the fifth and seventh most common cause of cancer death in Singaporean males and females, respectively.<sup>1</sup> This is because of the late presentation exhibited by most patients.

For early stage pancreatic cancer, surgery is the treatment modality of choice. Adjuvant chemotherapy has been proven to be of benefit for selected patients. For advanced pancreatic cancer, the treatment of choice is chemotherapy. Radiotherapy may be required in selected patients.

While several international guidelines for treatment of pancreatic cancer exist, due to unique differences in patient population, healthcare structure and reimbursement issues, direct application of these international guidelines to the local context is oftentimes not possible. Hence, there exists

a need to develop a set of local Singaporean guidelines to address this patient population and practice within our healthcare context.

## The SCAN Guidelines for the Management of Pancreatic Cancer

The SCAN Guidelines are clinical practice guidelines for the adjuvant and palliative management of pancreatic cancer (Table 1).

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for these management issues. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

## Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and

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Table 1. Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Pancreatic Adenocarcinoma

Guideline Recommendations	
Adjuvant Therapy for Resected Pancreatic Adenocarcinoma	<ol style="list-style-type: none"> <li>1. Adjuvant gemcitabine or adjuvant TS-1 are both reasonable options postsurgical resection for PDAC.</li> <li>2. Adjuvant radiation therapy concurrent with fluoropyrimidine is not recommended routinely for these patients unless resection margin is positive.</li> <li>3. A full restaging scan should be performed prior to start of adjuvant chemotherapy to rule out any metastases.</li> </ol>
Borderline Resectable Pancreatic Adenocarcinoma	<ol style="list-style-type: none"> <li>1. Neoadjuvant therapy can be considered in patients with borderline resectable pancreatic adenocarcinoma. There is insufficient evidence to recommend a specific regimen. Possible regimens for chemotherapy include FOLFIRINOX or gemcitabine-based combination chemotherapy. Subsequent chemoradiation can be considered after initial chemotherapy.</li> <li>2. Participation in clinical trials recommended if available.</li> </ol>
Locally Advanced Pancreatic Adenocarcinoma (LAPC)	<ol style="list-style-type: none"> <li>1. Chemotherapy alone or fluoropyrimidine-based chemoradiotherapy are reasonable options.</li> <li>2. Chemotherapy regimens recommended as per metastatic setting.</li> <li>3. Upfront chemoradiotherapy can be considered for patients with poorly controlled pain from local disease.</li> <li>4. Participation in clinical trials recommended if available.</li> </ol>
Metastatic Pancreatic Adenocarcinoma (PDAC)	<ol style="list-style-type: none"> <li>1. Best supportive care ought to be considered for patients with poor performance status.</li> <li>2. Systemic chemotherapy is recommended for patients with good performance status. First-line chemotherapy with FOLFIRINOX or combination gemcitabine and abraxane is preferred.</li> <li>3. In the second-line setting, the recommendation is fluoropyrimidine-based chemotherapy if previously treated with gemcitabine-based therapy or gemcitabine-based therapy if previously treated with fluoropyrimidine-based therapy.</li> <li>4. After second-line therapy, participation in clinical trials is recommended if available.</li> </ol>

general practitioners involved in the management of patients with pancreatic cancer.

### Guideline Recommendations/Development

The SCAN pancreatic cancer workgroup comprises a panel of 6 medical oncologists from Singapore with special subspecialty interest in the management of pancreatic cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework<sup>2</sup> was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, specific breast cancer-related issues of relevance were identified and the scope and distribution of tasks were finalised. High quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source

guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. The guidelines were chosen based on their high quality, currency and applicability to our patient population. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 4 main management issues which were selected for this topic:

1. Adjuvant Therapy for Resected Pancreatic Adenocarcinoma
2. Borderline Resectable Pancreatic Adenocarcinoma
3. Locally Advanced Pancreatic Adenocarcinoma (LAPC)
4. Metastatic Pancreatic Adenocarcinoma (PDAC)

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines in Pancreatic Ductal Adenocarcinoma” (version 1.2014) by the

National Cancer Comprehensive Network (NCCN, USA)<sup>3</sup>

- “Pancreatic Adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society of Medical Oncology (ESMO) 2012<sup>4</sup>
- “Program in Evidence-based Care (PEBC)” by Cancer Care Ontario 2013<sup>5-7</sup>
- “EBM-based Clinical Guidelines for Pancreatic Cancer (2013) Issued by the Japan Pancreas Society: A Synopsis” by the Japan Pancreas Society<sup>8</sup>
- “Guidelines for the Management of Patients with Pancreatic, Periampullary and Ampullary Cancers” by the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland and the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (2005)<sup>9</sup>

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of pancreatic cancer, it will be reviewed earlier.

## 1. Adjuvant Therapy for Resected Pancreatic Adenocarcinoma

### *Rationale for Adjuvant Chemotherapy after Resection of PDAC*

#### Gemcitabine or 5-fluorouracil (FU)

Even when R0 resection is achieved in pancreatic adenocarcinoma, relapse rates are still high. Only about 15% to 20% of PDACs are cured by resection alone. Several trials have examined the role of adjuvant chemotherapy given after resection in PDAC. The European ESPAC-1 trial was a large study examining adjuvant chemotherapy alone and chemoradiotherapy in resected PDAC.<sup>10</sup> In this 2x2 factorial design trial, adjuvant chemotherapy conferred better survival benefit compared to no chemotherapy (20.1 months vs 15.5 months,  $P = 0.009$ ). Adjuvant chemoradiotherapy did not improve survival compared to those who did not receive this. The subsequent CONKO-001 trial compared no adjuvant therapy to adjuvant gemcitabine after PDAC resection and showed improved 5-year overall survival (OS) of 11% (21% vs 10%) with addition of 6 months of adjuvant gemcitabine.<sup>11</sup> Similarly, a smaller Japanese trial also showed disease-free survival (DFS) benefit with adjuvant gemcitabine over observation.<sup>12</sup>

ESPA3 trial compared adjuvant gemcitabine with adjuvant bolus leucovorin-modulated 5-FU in resected PDAC and found no differences in survival outcomes between both arms.<sup>13</sup> However, patients who received fluoropyrimidines had more grade III and IV toxicities like stomatitis and

diarrhea. Similarly, in the RTOG 9704 trial, there were no survival differences between patients who received gemcitabine versus those who received fluoropyrimidines.<sup>14</sup>

The NCCN, ESMO and Canadian guidelines all recommend gemcitabine or 5-FU as adjuvant chemotherapy for resected PDAC.

#### TS-1

More recently, JASPAC-01 trial showed that adjuvant oral TS-1 alone was not inferior to adjuvant gemcitabine in resected PDAC.<sup>15</sup> Two-year survival with TS-1 was 70% and 53% with gemcitabine (HR = 0.54,  $P < 0.001$ ). TS-1 was also better tolerated than gemcitabine though the former had more incidences of stomatitis and diarrhea. The NCCN, ESMO and Canadian guidelines do not recommend TS-1 as adjuvant therapy as this drug is not available in some of these countries and TS-1 data in their PDAC populations is lacking.

All patients with resected PDAC should be considered for adjuvant therapy.

### *Role of Radiation Therapy as Part of Adjuvant Therapy*

In the 1980s, the GITSG trial that was conducted in the USA showed that adjuvant bolus 5-FU with radiation therapy (40 Gy) followed by adjuvant 5-FU for 2 years after PDAC resection doubled survival rates over observation alone (2-year OS, 20% vs 10%).<sup>16</sup> This trial was stopped early due to poor recruitment. The Europeans tried to reproduce these results in the EORTC trial done in the late 1990s, comparing continuous infusion 5-FU concurrent with split course radiation (40 Gy) therapy as adjuvant therapy with observation alone in resected PDACs.<sup>17</sup> This trial only showed a trend towards improved survival with chemoradiation and no differences in local recurrence.

The ESPAC-1 trial, which tried to compare adjuvant chemotherapy, adjuvant chemoradiation and observation found that patients who received adjuvant chemoradiation did worse than patients in the other groups.<sup>10</sup> Thus, based on EORTC and ESPAC-1, ESMO guidelines do not recommend adjuvant chemoradiation after PDAC resection. On the other hand, the American guidelines still recommend adjuvant chemoradiation based on the positive results of the GITSG trial and other uncontrolled series and the opinion that the flaws in the European trials preclude any firm conclusions.

### *Rationale for Postsurgery Imaging*

Pancreatic cancer has an extremely high rate of systemic recurrence (>80%) and a very high rate of local recurrence (>20%). Some patients develop recurrence within 8 weeks of surgery, thus it is recommended that imaging scans are

performed prior to initiation of adjuvant therapy. For patients for whom adjuvant chemoradiation is planned after adjuvant chemotherapy is started, an imaging scan is recommended prior to start of chemoradiation phase.

### Recommendations Regarding Adjuvant Therapy for Resected Pancreatic Adenocarcinoma

1. Adjuvant gemcitabine or adjuvant TS-1 are both reasonable options postsurgical resection for PDAC.
2. Adjuvant radiation therapy concurrent with fluoropyrimidine is not recommended routinely for these patients unless resection margin is positive.
3. A full restaging scan should be performed prior to start of adjuvant chemotherapy to rule out any metastases.

### 2. Borderline Resectable Pancreatic Adenocarcinoma

The consensus statement from the American Hepato-Pancreato-Biliary Association (AHPBA)<sup>18</sup> which is also endorsed by NCCN<sup>3</sup> and ESMO<sup>4</sup> considered “borderline resectable pancreatic adenocarcinoma” to include the following:

1. No distant metastases.
2. Venous involvement of the superior mesenteric vein (SMV)/portal vein demonstrating tumour abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumour thrombus or encasement, but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
3. Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct tumour abutment of the hepatic artery, but without extension to the celiac axis.
4. Tumour abutment of the superior mesenteric artery not to exceed  $>180^\circ$  of the circumference of the vessel wall.

There is no clear consensus with regard to management of borderline resectable pancreatic adenocarcinoma. NCCN and ESMO guidelines consider neoadjuvant therapy as an acceptable option to upfront resection in patients with borderline resectable pancreatic cancer. There is however insufficient evidence to recommend specific neoadjuvant regimens. PEBC, Cancer Care Ontario (CCO), the Japan Pancreas Society (JPS) and the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland and the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) recommend participation in clinical trials where possible in this instance.

### Recommendations for Borderline Resectable Pancreatic Adenocarcinoma

1. Neoadjuvant therapy can be considered in patients with borderline resectable pancreatic adenocarcinoma. There is insufficient evidence to recommend a specific regimen. Possible regimens for chemotherapy include FOLFIRINOX or gemcitabine-based combination chemotherapy. Subsequent chemoradiation can be considered after initial chemotherapy.
2. Participation in clinical trials recommended if available.

### 3. Locally Advanced Pancreatic Adenocarcinoma (LAPC)

At initial diagnosis, 30% of patients with pancreatic adenocarcinoma present with locally advanced tumour (LAPC).<sup>19</sup> The goals of treatment are to reduce symptoms and prolong life. Treatment recommendation depends on the patient’s performance status. Patients with poor performance status would not benefit from aggressive therapy. The following discussion is meant for patients with good performance status.

#### *Chemotherapy versus Chemoradiotherapy*

There are differing treatment recommendations. Both NCCN and ESMO guidelines recommend systemic chemotherapy alone, although NCCN does endorse chemoradiotherapy following a course of systemic chemotherapy in selected patients. PEBC, CCO prefers chemoradiotherapy whilst JPS lists chemoradiotherapy as an option.

The utility of adding radiotherapy to chemotherapy is debatable. Two chemoradiotherapy strategies have been employed: 1) upfront chemoradiotherapy and 2) chemoradiotherapy following chemotherapy.

#### *Upfront Chemoradiotherapy*

Two recent studies have evaluated the role of upfront chemoradiotherapy in this setting with differing conclusions. Both studies were however terminated early. ECOG 4201 compared gemcitabine alone versus gemcitabine with radiotherapy in patients with LAPC. Despite poor accrual and early termination, median OS of patients who received radiotherapy was longer (9.2 months vs 11.1 months,  $P = 0.017$ ). This study however lacks statistical robustness as the confidence interval of survival between the 2 arms overlap.<sup>20</sup>

The FFCO-SFRO study randomised 119 patients to receive either gemcitabine alone or intensive chemoradiotherapy with 5-FU plus cisplatin followed by maintenance gemcitabine. This study demonstrated a superior OS at 1 year for gemcitabine alone compared to chemoradiotherapy

(53% vs 32%, HR = 0.54; 95% CI, 0.31 to 0.96;  $P = 0.006$ ). This study was stopped early as interim analysis showed a lower survival rate in combination arm attributable to increased severe toxicities.<sup>21</sup>

Taken together, upfront chemoradiotherapy in patients with LAPC is controversial. Use of upfront chemoradiotherapy however, can be considered in selected cases, for example in patients with poor pain control.

#### *Chemoradiotherapy Following Chemotherapy*

The LAP 07 trial attempted to evaluate the additional benefit of chemoradiotherapy after a course of chemotherapy. Preliminary analyses have been presented in abstract form. LAPC patients were first randomised to gemcitabine or gemcitabine plus erlotinib. Patients with controlled disease after 4 months of chemotherapy were then randomised to 2 additional months of chemotherapy or chemoradiotherapy amounting to 54 Gy and concurrent capecitabine. Administration of chemoradiotherapy in patients with LAPC controlled with induction chemotherapy was not superior to continuing chemotherapy alone in terms of overall survival. The OS was not significantly different between the 2 arms (15.2 vs 16.5 months,  $P = 0.8$ ). Even though the OS was not improved in the chemoradiotherapy arm, patients with non-progressive LAPC after 4 months of induction chemotherapy had a longer time without treatment in the chemoradiotherapy arm (159 vs 96 days, respectively,  $P = 0.05$ ) with significantly less local tumour progression (34% vs 65%,  $P < 0.0001$ ).<sup>22</sup>

#### *Choice of Chemotherapy*

Choice of chemotherapy used in patients with LAPC mirrors the options of systemic chemotherapy in the metastatic setting.

### **Recommendations for LAPC**

1. Chemotherapy alone or fluoropyrimidine-based chemoradiotherapy are reasonable options.
2. Chemotherapy regimens recommended as per metastatic setting.
3. Upfront chemoradiotherapy can be considered for patients with poorly controlled pain from local disease.
4. Participation in clinical trials recommended if available.

### **4. Metastatic Pancreatic Adenocarcinoma**

#### *Front-line Treatment for Metastatic Pancreatic Adenocarcinoma (PDAC)*

Patients with poor performance status ought to be offered the best supportive care. In younger patients with good

performance status, options for first-line chemotherapy that have emerged in more recent studies include FOLFIRINOX<sup>23</sup> and gemcitabine in combination with nab-paclitaxel.<sup>24</sup> This is based on the PRODIGE<sup>23</sup> and MPACT<sup>24</sup> trials respectively, first-line radiochemotherapies (RCTs) showing overall survival benefits when compared to the existing standard of gemcitabine monotherapy.<sup>25</sup>

FOLFIRINOX has shown an improvement in both median progression-free survival (PFS) (6.4 months vs 3.3 months,  $P < 0.001$ ) and median OS (11.1 months vs 6.8 months,  $P < 0.001$ ). The rates of grade III or IV toxicities were higher in the FOLFIRINOX arm, in particular 45.7% for neutropenia, though there were no toxic deaths reported. In fact, the patients in the FOLFIRINOX arm had an improved quality of life comparatively.<sup>25</sup> The toxicities of FOLFIRINOX could be managed with supportive measures such as growth factor support.

The MPACT trial<sup>24</sup> showed that the addition of nab-paclitaxel to gemcitabine demonstrated improved median OS (8.5 months vs 6.7 months;  $P < 0.0001$ ), median PFS (5.5 months vs 3.7 months;  $P < 0.001$ ) and improved overall response rate (ORR) (23% vs 7%;  $P < 0.001$ ). The common grade III or IV adverse events attributable to nab-paclitaxel were neutropenia (38%), fatigue (17%), and neuropathy (17%).

For older patients and individuals who are unable to tolerate combination therapy, it is reasonable to consider monotherapy with either gemcitabine or S-1.<sup>26-27</sup>

#### *Addition of Targeted Therapy to Systemic Chemotherapy*

There is currently no evidence to support the use of targeted therapy with bevacizumab or cetuximab in combination with chemotherapy in the first-line treatment of metastatic pancreatic carcinoma.

#### *Second-line Treatment*

In the second-line setting, for patients with good performance status, fluoropyrimidine-based chemotherapy is recommended for patients who had previously been treated with gemcitabine based therapy<sup>7-9,28-30</sup> or gemcitabine-based therapy if previously treated with fluoropyrimidine-based therapy.<sup>30</sup>

A systemic review of clinical trials done in the second-line setting revealed that there is limited data but possible advantage of second-line treatment over best supportive care.<sup>30</sup>

#### *Third-line Treatment*

Patients who have progressed beyond 2 or more lines of treatment are recommended for enrollment in clinical trials if they still have good performance status.

## Recommendations for Metastatic Pancreatic Cancer

1. Best supportive care ought to be considered for patients with poor performance status.
2. Systemic chemotherapy is recommended for patients with good performance status. First-line chemotherapy with FOLFIRINOX or combination gemcitabine and abraxane is preferred.
3. In the second-line setting, the recommendation is fluoropyrimidine-based chemotherapy if previously treated with gemcitabine-based therapy or gemcitabine-based therapy if previously treated with fluoropyrimidine-based therapy.
4. After second-line therapy, participation in clinical trials is recommended if available.

All recommendations were unanimously agreed upon.

### Conflicts of Interest

*Dr Choo reports serving on advisory boards of Bayer, Novartis, Bristol Myers Squibb and Lilly Oncology, receiving advisory or speaker honoraria from SIRTEX, Novartis and Bristol Myers Squibb and travel funding from Merck; Dr Lim, receiving advisory board fees from Pfizer and Bristol Myers Squibb and speaker bureau fees from Novartis; Dr Yeo, serving on advisory boards of Roche and Bayer; Dr Yong, receiving fees from Roche as a trial data safety monitoring committee member; Dr Foo and Dr Tai have nothing to disclose.*

### Workgroup Members

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### Reviewers

*Invited reviewers were Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; John Zalcberg, MBBS, PhD, FRACP, Cancer Research Program, Monash University, Australia; Eileen M O'Reilly, MD, Department of Medicine, Memorial Sloan Kettering Cancer Center, USA; Junji Furuse, MD, PhD, Department of Medical Oncology, Kyorin University School of Medicine, Japan; Takuji Okusaka, MD, PhD, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Japan.*

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Supplementary Table 1. International Guidelines for Systemic Therapy of Pancreatic Adenocarcinoma

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Pancreatic Ductal Adenocarcinoma Cancer Version 1.2014	Pancreatic Adenocarcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Guidelines for the Management of Patients with Pancreatic Cancer, Periampullary and Ampullary Carcinoma	Program in Evidence-Based Care (PEBC), Cancer Care Ontario	EBM-Based Clinical Guidelines for Pancreatic Cancer 2009 from the Japan Pancreas Society: A Synopsis	Singapore Cancer Network (SCAN) Guidelines
Date Released	1 January 2014	1 October 2012	13 May 2005	2 April 2013	1 July 2009	27 March 2014
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	Pancreatic section of the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Royal College of Pathologists, Special Interest Group for Gastro-Intestinal Radiology	Cancer Care Ontario (CCO)	Japan Pancreas Society	Consensus of SCAN Pancreatic Cancer Workgroup
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment.	Recommendations developed from discussion at consensus conferences. Group decision-making that seeks the consensus of experts and the fulfillment of objectives.	Consensus statement of authors based on available evidence.	Recommendations derived from systematic review of clinical and scientific literature and its interpretation by Disease Site Group (DSG) or Guideline Development Group (GDG) and a formalised external review by Ontario practitioners.	Recommendations derived from systematic review of literature listed on PubMed and Igakuchuo Zasshi (443 papers).	Recommendations made through adaptation of existing guidelines.
Target Population	Preoperative Panel does not recommend neoadjuvant therapy for resectable patients except on a clinical trial. For selected patients who appear technically resectable but have poor prognostic feature, however, consideration can be given to neoadjuvant therapy after biopsy confirmation though a clinical trial is preferred.	Preoperative In case of resectable pancreatic cancer, neoadjuvant chemotherapy, radiotherapy or chemoradiation should only be performed within clinical trials. Patients should be encouraged to join clinical trials.	Preoperative Neoadjuvant therapies should only be given within the context of a clinical trial.	Preoperative There is insufficient evidence to support the use of preoperative chemotherapy or radiotherapy.	Preoperative There is increasing evidence supporting the efficacy of preoperative treatment: 1) chemotherapy and 2) clinical trials or long-term analyses are required.	Preoperative Patients with resectable pancreatic adenocarcinoma should undergo upfront resection*.
Treatment						

\*Resectable – resect first.

†Borderline – consider neoadjuvant, insufficient evidence to recommend specific regimen.

‡Chemotherapy or chemoRT.

§Possible regimens: FOLFIRINOX, GEM-based treatment.

Supplementary Table 1. International Guidelines for Systemic Therapy of Pancreatic Adenocarcinoma (Cont)

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Pancreatic Ductal Adenocarcinoma Cancer Version 1.2014	Pancreatic Adenocarcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Guidelines for the Management of Patients with Pancreatic Cancer, Periampullary and Ampullary Carcinoma	Program in Evidence-Based Care (PEBC), Cancer Care Ontario	EBM-Based Clinical Guidelines for Pancreatic Cancer 2009 from the Japan Pancreas Society: A Synopsis	Singapore Cancer Network (SCAN) Guidelines
Treatment	<p>Many NCCN member institutions and the panel itself consider neoadjuvant therapy as an acceptable option to upfront resection in patients with borderline resectable pancreatic cancer. There is insufficient evidence to recommend specific neoadjuvant regimens.</p>	<p>Patients with borderline resectable pancreatic cancer may benefit from neoadjuvant chemotherapy or chemoradiotherapy. The optimal neoadjuvant strategy is still under investigation and there is no standard protocol for neoadjuvant chemoradiotherapy in Europe.</p>	<p>Patients with borderline resectable pancreatic cancer may benefit from neoadjuvant chemotherapy or chemoradiotherapy. The optimal neoadjuvant strategy is still under investigation and there is no standard protocol for neoadjuvant chemoradiotherapy in Europe.</p>			<p>Neoadjuvant chemotherapy or chemoradiotherapy can be considered in patients with borderline resectable pancreatic cancer<sup>†</sup>. There is insufficient evidence to recommend a specific regimen. Possible regimens for chemotherapy include FOLFIRINOX or gemcitabine-based combination chemotherapy<sup>§</sup>.  Participation in clinical trials recommended if available.</p>

\*Resectable – resect first.

<sup>†</sup>Borderline – consider neoadjuvant, insufficient evidence to recommend specific regimen.

<sup>‡</sup>Chemotherapy or chemoRT.

<sup>§</sup>Possible regimens: FOLFIRINOX, GEM-based treatment.