Informed Decision Making for Patients With Advanced Pancreatic Cancer Considering Chemotherapy: Development and Evaluation of a Clinical Decision Aid for Patients

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ABSTRACT

Pancreatic cancer is the fourth leading cause of cancer death in Canada. Significant advancements in chemotherapy for advanced pancreatic cancer have resulted in the need for a quantitative comparison between these treatments on a relative scale. Therefore, a systematic review and Bayesian network meta-analysis of randomized clinical trials was conducted using gemcitabine, the standard treatment, as the reference comparator. Based on results from the network meta-analysis, in which optimal treatments were identified and side effects of each treatment evaluated, an Internet-based patient decision aid was developed in order to present the benefits and risks of each therapy option: (1) Best supportive care (2) gemcitabine (3) FOLFIRINOX. The objective of the decision aid was to guide patients through the decision-making process based on their individual preferences and values. The decision aid was deemed to be acceptable and feasible based on results from a pilot study conducted at The Ottawa Hospital Cancer Centre.

EXECUTIVE SUMMARY

Background: Pancreatic cancer is a devastating disease that is responsible for almost as many deaths as diagnoses each year. Due to the late onset of symptoms, and rapid progression of the disease, most cases are diagnosed at an advanced stage, where there is no option for cure. Prognosis is poor with a 5-year overall survival of only 1.8% in patients with advanced pancreatic cancer. Despite efforts to develop effective treatments to improve survival rates, progress has been slow. Over the past decade, where over twenty treatments have been tested in randomized clinical trials, most studies have been negative offering only marginal improvements in survival outcomes. However, in the past couple years, promising results from new regimens including FOLFIRINOX and the combination of gemcitabine and NAB-Paclitaxel, have established a need for a quantitative comparison between these treatments on a relative scale. There is also a strong need to communicate this information to patients in a way that allows them to share the decision-making process with their oncologists, as patients have become more engaged in making important treatment decisions.

Methods: A systematic review of all phase III randomized clinical trials that met quality standards and compared chemotherapy regimens to gemcitabine, the standard first-line therapy for advanced pancreatic cancer over the past decade. Hazard ratios for overall survival, progression free survival and safety outcomes were indirectly compared through a Bayesian network meta-analysis using gemcitabine as the reference comparator. Based on findings from the most current systematic reviews and meta-analyses, the need for the development of a decision tool to guide patients through the decision-making process was also established. Consequently, the design and development of an Internet-based patient decision aid was developed for patients with advanced pancreatic cancer in order to communicate the results of the network meta-analysis in a comprehensive and transparent manner. The development of the decision aid followed the IPDAS criteria checklist within the scope of The Ottawa Decisional Support Framework (ODSF). Founded on the results of the network meta-analysis, FOLFIRINOX was presented the more aggressive treatment option in the decision aid. Gemcitabine was also included as an option, being the standard treatment for advanced pancreatic cancer, and associated with fewer side effects. The option of best supportive care alone was provided for

patients who may choose not to pursue chemotherapy treatment. Benefits and risks of each treatment were displayed as visual diagrams for each outcome. All numerical probabilities were reported with accompanying written and visual descriptions. The patient decision guide was divided into six components: overall survival; cancer control; side effects; symptom control; and convenience. Upon completion of the development phase of the decision aid, a pilot study was then designed to evaluate this intervention in a healthcare setting. With ethics approval from the Ottawa Hospital Research Ethics Board, a single-center, single arm prospective observational study was conducted. The primary purpose of this pilot study was to evaluate the overall acceptability and feasibility of the decision aid, using adapted questionnaires for the outcomes of interest, which were administered after the distribution of the decision aid and first consultation visit with the medical oncologist.

Results: In the systematic review, and network meta-analysis, 23 studies were included in the analysis. FOLFIRINOX was associated with statistically significant hazard ratios for overall survival and progression free survival for 15/19 treatments, being ranked first (1.47/19) with the highest probability of being best (65%). FOLFIRINOX was associated with an overall survival gain of 4 months over gemcitabine alone. A network meta-analysis of grade 3/4 adverse events of treatments found FOLFIRINOX to be associated with significantly greater grade3/4 neutropenia over other treatments including gemcitabine+nab-paclitaxel. Gemcitabine plus nab-paclitaxel was found to have a trend towards a statistically significant increase of odds for grade 3 or 4 fatigue over FOLFIRINOX. In a sensitivity analysis for performance status, FOLFIRINOX was excluded from the analysis, and gemcitabine+nab-paclitaxel was associated with the greatest survival outcomes. Based on these findings, results were displayed in the web-based information guide and decision aid for patients with pancreatic cancer and piloted in an observational study at The Ottawa Hospital Cancer Center. Results from the pilot study suggest that a small group of selected metastatic pancreatic cancer patients found that the decision aid was acceptable and feasible and that the information was presented in an objective and balanced manner.

Conclusions: Overall, FOLFIRINOX was associated with superior survival outcomes to the majority of gemcitabine based combinations and should be included as a primary option to

patients who can tolerate it. Information about the associated benefits and risks of the treatment, however, need to be shared and communicated with patients in a way that allows them to weigh their options and decide on a treatment that suits their preferences and values. As no decision tool exists for this particular population of patients, and it was unclear whether there was a need for a decision aid in this population, a pilot study of the decision aid was conducted. Both patients and practitioners confirmed that there was a need for a decision aid for patients with advanced pancreatic cancer, and that the presented decision aid was acceptable and feasible. The design of a prospective randomized clinical trial comparing this decision aid to a standard pamphlet can now be considered to further test the decision aid's impact on patient outcomes such as knowledge and decisional conflict.

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TABLE OF ABBREVIATIONS:

5FU	5-fluorouacil
aPC	Advanced pancreatic cancer
AE	Adverse Event
CT	Computed Tomography
FOLFIRINOX	Folinic acid plus 5-fluorouacil plus Irinotecan plus oxaliplatin
Gem	Gemcitabine
Gem+NAB-P	Gemcitabine plus NAB-Paclitaxel
IPDAS	International Patient Decision Aid Standards
MRI	Magnetic Resonance Imaging
NAB	130 nm albumin-bound
OSDF	Ottawa Decision Support Framework
ORR	Overall Response Rate
OS	Overall Survival
PtDA	Patient Decision Aid
PFS	Progression Free Survival
QOL	Quality of Life
RCT	Randomized Controlled Trial

1. INTRODUCTION

1.1. Rationale

"When your values are clear to you, making decisions becomes easier."-R.E.Disney

Shared decision making arises from a patient's desire to be an active participant in the decision making process, and the physician's reciprocal willingness to share the decision with their patients. As it is outlined in the patient bill of rights, all patients possess the right to know and take part in any decisions surrounding their health care. Patients equally have corresponding responsibilities to ask questions, follow instructions, understand their treatment plan and request information. Thus, patients require high quality and accurate information about their treatment options in order to make informed decisions about their care. The need for objective and current research that is accessible and comprehensible to the patient population bolsters the development of additional support tools, such as decision aids, to help inform patients about their treatment options and guide them through the decision making process. The primary purpose of a decision aid is to present complete evidence-based information on different treatment options in an objective and balanced manner that allows patients to measure the associated benefits against the risks in order to make a decision based on their own individual preferences and values.

Decisions become more complex when patients are being faced not only with several different treatment types to choose from, but also the option of best supportive care alone. Such is the case for patients with advanced cancers, where their disease has spread to other parts of their body and there is no option for cure. Patients in this scenario often face additional decisions about end of life care. Furthermore, they must make the decision as to whether a marginal increase in survival time is worth the additional side effects that they may experience.

By identifying the need for further research, and the complexity of decisions that patients with advanced pancreatic cancer face, it was of interest to develop a decision tool to help educate patients on the different treatment options available to them, and guide them through the difficult treatment decisions.

1.2. Outline and objectives

This thesis was divided into three phases where evidence-based knowledge was first reviewed and evaluated through a systematic review of the literature and network meta-analysis. Results from the network meta-analysis were then used to develop a patient decision aid for patients with advanced pancreatic cancer considering chemotherapy. To determine its acceptability and feasibility, the decision aid was then piloted in a prospective observational study. Each chapter of the thesis summarizes the background information, methodology, results and discussion associated with the respective phase of the project.

An overview of the specific objectives of each of the thesis chapters are outlined below:

Chapter 1: Introduction

This chapter presented a general introduction to the ideas that were discussed in the thesis as well as an overview of the primary objectives of each of the included chapters.

Chapter 2: Background

Important background information on advanced pancreatic cancer and its therapeutic management was presented. A detailed description on patient decision aids was also provided in order to inform readers about the disease, its treatment and the application of decision aids in a way that allows them to appreciate and understand the content of the subsequent chapters.

Chapter 3: Gathering the evidence: A systematic review and network meta-analysis of treatments available for advanced pancreatic cancer.

The first phase of the thesis included the review and evaluation of the evidence-based knowledge for survival and safety outcomes as compared in randomized clinical trials of patients with advanced pancreatic cancer treated with chemotherapy. In the absence of direct evidence, indirect comparisons were accomplished using a Bayesian network meta-analysis. Effect estimates for each indirect comparison were obtained where the optimal therapies were identified in order to present as treatment options in the patient decision aid.

Chapter 4: Design and development of a patient decision aid: An internet-based clinical decision aid for patients with advanced pancreatic cancer considering chemotherapy

An Internet-based patient decision aid for patients with advanced pancreatic cancer was designed and developed using information extracted from the systematic review and network meta-analysis. This interactive decision aid was designed to provide information on the advantages and disadvantages that each treatment option presents and to guide patients through the decision making process.

Chapter 5: Evaluating the intervention: Needs assessment and pilot study of a decision aid for patients with advanced pancreatic cancer considering chemotherapy

The final phase of the thesis involved the needs assessment and evaluation of the decision aid. A prospective pilot study of the decision aid was designed and conducted in order to evaluate the overall acceptability and feasibility of the decision aid that was designed in the previous chapter. The impact of the developed clinical decision aid on outcomes such as patient knowledge, realistic expectations, and decisional conflict was explored.

Chapter 6: Overall Summary and Recommendations

This chapter summarizes the key conclusions of each individual chapter as well as the overall conclusion of the thesis as a whole. Applications and implications of the research conducted for this thesis, namely the use of a patient decision aid for patients with pancreatic cancer, were emphasized. The chapter concludes with the discussion of future directions and recommendations for the different components of this project.

2. BACKGROUND

2.1. Pancreatic cancer

2.1.1. Epidemiology of pancreatic cancer

Pancreatic cancer is a deadly disease that claims the lives of thousands of people each year. Although it is the twelfth most commonly diagnosed cancer in Canada, with 4600 new diagnoses in 2012, it has remained the fourth leading cause of cancer death with 4200 deaths within the same year for both males and females[1]. Pancreatic cancer is also ranked the fourth deadliest disease in the United States of America as well as worldwide[2]. Although surgical resection offers hope for cure, 85-90% of the presenting cases are either advanced or metastatic at diagnosis due to the disease's late onset of symptoms[3]. This results in a five year overall survival rate of only 2%[3]. The lifetime risk of developing pancreatic cancer is about 1.5% for both males and females, where the distribution of the disease across sexes is relatively equal with a slightly higher incidence in males[3]. Incidence of pancreatic cancer varies across races, where African Americans and people with Ashkenazi Jewish heritage are at greater risk of developing the disease[4, 5]. The lowest rates are observed in Asian Americans and Pacific Islanders. Between 2005-2009, the incidence rate, per 100,000 persons was 15.3 for African Americans, 11.6 for Caucasians and 11.6 for Asian Americans[3]. Incidence also increases with age, where adults between the ages of 60 and 80 are most often diagnosed, with a median age at diagnosis of 71 years[2]. Socioeconomic status has also been thought to have an impact on mortality rates from pancreatic cancer where studies have found that fewer years of education and lower income were associated with increased risk of pancreatic cancer[3].

2.1.2. Causes of pancreatic cancer

The exact causes of pancreatic cancer are not well understood although some modifiable risk factors such as smoking, obesity, diabetes, and pancreatitis are thought to contribute to an increased risk of pancreatic cancer. Tobacco use is the most important known risk factor for pancreatic cancer, where 20% of diagnoses can be attributed to cigarette smoking[5]. Obesity has also been linked to a 20%

increased risk of developing pancreatic cancer in comparison to those belonging to a normal weight category[3]. Certain dietary consumption such as heavy alcohol intake or meat consumption are associated with an increased risk while folate intake and vitamin D consumptions is associated with protective effect on pancreatic cancer. There is also a familial component to the risk of pancreatic cancer where 5-10% of diagnoses are attributed to hereditary causes and can be categorized as familial risk and germ line mutations[6]. Genetic factors including mutations of the BRCA1, BRCA2 gene and CDKN2A gene have been shown to be linked to pancreatic cancer[3]. Peutz-Jeghers Syndrome, which is an autosomal dominant polyposis disorder caused by mutations in the STK11 gene, has also been found to increase the risk of developing pancreatic cancer[7, 8]. Other syndromes such as Hereditary Nonpolyposis Colon Cancer (HNPCC), Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM), Familial Adenomatous Polyposis (FAP) and Hereditary Pancreatitis, which are all autosomal dominant conditions often associated with increased risk of colorectal cancers, have also been linked to a higher risk of developing pancreatic cancer[6].

2.1.3. Diagnosis of pancreatic cancer

The dilemma involved with the diagnosis of pancreatic cancer consists of a very early and rapid spread of the disease, but a late diagnosis, due to its insidious character. The late onset of symptoms and lack of valid tests to screen or detect pancreatic cancer in its earlier stages, results in 85-90% of the patient population being diagnosed with advanced unresectable disease[3]. Common symptoms experienced by patients diagnosed with pancreatic cancer include but are note limited to pain, jaundice, fatigue, weight loss, nausea or vomiting, diarrhea and constipation. Some patients also experience sudden onset of Type II diabetes. However, not all patients will experience these symptoms and it is not uncommon for patients to be asymptomatic throughout the progression of their disease. Upon the onset of symptoms, physical examination of the patient may help identify the need for further imaging where detection of the disease is most commonly accomplished using CT scans or Magnetic Resonance Imaging (MRI). Scans can help physicians determine the primary location and size of the tumour and whether it has metastasized while biopsies will further identify the pathology of the disease. Depending on its pathology, and whether the disease has spread, different treatment options may be available to the patient. Patients can be diagnosed with either exocrine or endocrine pancreatic

cancer, although the majority of cases (95%) evolve from the exocrine pancreas. There are four stages of pancreatic disease used to describe the extent that the tumour has spread to other adjacent or distant organs (Table 1)[9]. Depending on the aggressiveness of the tumour, sub-stages also exist to further describe the exact nature of the disease. While Stage 0-III disease can be cured with surgical resection of the tumour, surgery is not a viable option for patients with advanced cancer including unresectable stage III or stage IV diagnosis.

Table 1: Pancreatic cancer staging based on the UICC staging system[9]

UICC stage	Explanation
Stage 0	Abnormal cells are found only in the lining of the pancreas (also called carcinoma in situ).
Stage IA	Tumour is only in the pancreas and is 2 cm or less.
Stage IB	Tumour is only in the pancreas and is larger than 2 cm.
Stage IIA	Tumour has spread to nearby tissues but not to nearby large blood vessels.
Stage IIB	Tumour is in the pancreas or has spread to nearby tissues but not to nearby large blood vessels. There is spread to regional lymph nodes.
Stage III	Tumour has spread beyond the pancreas into nearby large blood vessels. There may be spread to regional lymph nodes.
Stage IV	The cancer has spread to distant sites, such as the liver, lung

While the five year overall survival for patients with stage one or two resected disease ranges between 15-20%, the survival rates for patients with locally advanced stage three is 5%, and metastatic stage four is only 2%[3]. Distinguishing between locally advanced and metastatic pancreatic cancer, locally advanced disease refers to pancreatic tumours that have invaded important structures, veins or arteries in the pancreas and cannot be surgically removed without compromising these structures,

while metastatic pancreatic cancer indicates that the cancer has spread to distant organs such as the liver, lungs, stomach, etc.

With little known about the causes of the disease, no valid screening tools currently available to detect the disease at an earlier stage, and only stepwise improvements in the development of treatments available for the disease, there is a strong desire to help patients diagnosed with this devastating disease.

2.2. Therapeutic management of pancreatic cancer

A multidisciplinary approach is often used for patients with pancreatic cancer where they are seen by surgeons, radiation oncologists and medical oncologists for the consideration of multimodality treatment. Additionally, gastroenterologists, pain management experts, nutritionists, social workers and other members of the health care staff work together to manage the symptoms caused by pancreatic cancer and any side effects related to its treatment. Surgical resection of the pancreatic tumour offers the only hope for cure of the disease. Unfortunately, only about 10-15% of presenting cases are deemed to be resectable, while the remaining cases are diagnosed with either advanced or metastatic pancreatic disease[3].

2.2.1. Chemotherapy

Systemic chemotherapy has had the greatest impact on survival for advanced pancreatic cases, although only modest improvements in survival outcomes have been observed over the past two decades. However, there have been some advances made in the therapeutic management of metastatic pancreatic with chemotherapy. Chemotherapy is the use of drugs to kill cancer cells by interfering with their ability to replicate and spread. Chemotherapy, in the form of monotherapy or combination therapy, is the recommended first-line therapy for patients with advanced pancreatic cancer.

2.2.1.1. Single-agent Gemcitabine in the therapeutic management of pancreatic cancer

Gemcitabine, (2,2 difluoro deoxycytidine) was approved for first-line therapy in 1997 when it was reported to show a statistically and clinically significant survival benefit over 5-fluourouacil[10]. It is a pyrimidine antimetabolite that has been found to have good activity in various solid tumours[11]. Gemcitabine has since been the recommended standard treatment for advanced pancreatic cancer as it is associated with good treatment tolerability and low risk for side effects. However, due to the marginal impact it has made on patient survival outcomes, oncologists have subsequently explored combination therapy as another treatment option.

2.2.1.2. Combination Therapy with Gemcitabine as a backbone

A myriad of efforts have been made to combine Gemcitabine with other therapies in order to improve prognosis. Up to date, many studies have evaluated the addition of a second cytotoxic agent on survival outcomes. A meta-analysis conducted by Hu *et al* supports the additional survival benefit associated with combination chemotherapy regimens[7]. First, gemcitabine has been combined with platinum analogs such as cisplatin or oxaliplatin to accomplish synergistic cytotoxicity, which results from DNA repair inhibitory property of gemcitabine[11]. Although a handful of trials have been conducted to compare gemcitabine plus platinum analogs to gemcitabine alone, individual trials have shown no statistically superior differences in survival outcomes. However, there have been statistically significant improvements in overall survival detected when combined in meta-analyses[12, 13]. Fluoropyrimidines have also been combined with gemcitabine in the forms of 5-fluorouacil (5-FU) and capecitabine. Preclinical studies have shown that the combination of gemcitabine and 5-FU has resulted in synergistic interactions between the two antimetabolites, where gemcitabine increases 5-FU activity by depletion of cellular deoxyuridine monophosphate pools and inhibition of thymidylate synthase, while 5-FU prevents the inactivation of gemcitabine monophosphate by deamination[11, 12]. No trials to date comparing gemcitabine with gemcitabine plus 5-FU have resulted in statistically superior survival outcomes. On the other hand, capecitabine, another fluouropyrimidine, has been found to have statistically superior survival outcomes when combined with gemcitabine in comparison to gemcitabine alone[14-16]. The combination of gemcitabine with topoisomerase inhibitors including

Irinotecan and Docetaxel, has also been explored where no statistically significant benefits were observed[18,19]. More recently, research has expanded to include the combination of gemcitabine with various targeted therapies such as cetuximab, tipifarnib, axinitib and erlotinib, which were all associated with negative results except for a slight survival benefit observed in the combination of gemcitabine plus erlotinib[20-23]. The survival benefit of gemcitabine plus erlotinib was found to be greater when combined with bevacizumab, in a phase III trial published in 2009[24]. A small number of trials have also explored the combination of gemcitabine with matrix metalloprotease inhibitors such as marismastat[25]. Marismastat is a zinc-dependent enzyme involved in remodelling and turnover of extracellular matrix proteins[12].

Most recently, in January 2013, promising results from a phase three randomized clinical trial comparing gemcitabine alone to gemcitabine combined with a new drug, NAB-Paclitaxel, has peaked some interest around the idea of introducing this treatment as a new standard[26]. NAB-paclitaxel provides tumour selective localization and potential uptake as well as improved pharmokinetics[26]. It has shown promising activity in phase I and II studies and has been most recently tested in a large phase III RCT. NAB-Paclitaxel was found to have a statistically significant survival benefit over gemcitabine alone, with a median survival time of 8.5 months and was also thought to be associated with less significant toxicities than FOLFIRINOX, a four-drug combination therapy discussed in detail in the following section. Being presented at an oral presentation at a large cancer meeting, efforts were made to compare these two promising treatments in terms of survival and safety outcomes, although such comparisons cannot effectively be accomplished without a proper head-to-head trial. The interest in comparing these two treatments amongst others provided supplemental rationale for conducting a network meta-analysis to indirectly compare the different treatments amongst others, to inform physicians and patients about the optimal therapy and assist them in the decision making process.

2.2.1.3. Four-drug combination therapies

The decade-long search to optimize gemcitabine efficacy resulted in the undertaking of a more aggressive approach to the design of combination drugs; moving forwards from coupled therapies to multi-drug therapies. The combination of four drugs to treat advanced pancreatic cancer has shown to

provide the best survival outcomes. In 2005, Reni *et al.* performed a four-drug study, which included gemcitabine, cisplatin, epirubicin and 5-FU[27]. The combination of these drugs, known as the PEFG regimen, was found to increase efficacy. This small phase III trial resulted in a statistically significant increase in survival outcomes including overall survival, progression free survival and overall response rate. These promising results lead to the development of other four-drug combination therapies. However, the resulting negative studies from gemcitabine-based combination therapies and the need to identify an optimal therapy that is associated with greater survival outcomes, lead researchers away from the gemcitabine backbone to other possible combinations of treatments, including the most recent combination of folinic acid (FOL), 5-FU (F), Irinotecan (IRIN) and Oxaliplatin (OX), FOLFIRINOX.

FOLFIRINOX was approved in Ontario (November 2011) to treat metastatic pancreatic cancer[28]. To date, there has been a phase two and phase three trial of FOLFIRNIOX versus gemcitabine published by the same authors[28, 29], where the results from the phase three RCT were published in May 2011. This trial randomly assigned 342 patients to either gemcitabine or FOLFIRINOX across 48 centers in North America[28]. FOLFIRINOX was found to be associated with significant survival advantage ($p<0.0001$) and median survival of 11.1 months. However, it was also found to be associated with significant toxicities including neutropenia, febrile neutropenia, thrombocytopenia, neuropathy, diarrhea, appetite loss and constipation. This leads to the question of whether the survival benefit of FOLFIRINOX outweighs the added risks and toxicities. Nonetheless, FOLFIRINOX has become the more recommended form of chemotherapy for patients who can tolerate it.

2.2.2. Pancreatic cancer management with best supportive care

The persistence of symptoms throughout the patient's course of the disease calls for the focus of care around relieving and preventing suffering[30-32]. Poor survival rates and minimal response to treatment associated with the disease, reinforce the need to manage and control the patient's symptoms. Palliative care should be offered to a patient regardless of whether they opt for treatment or not, in order to relieve symptoms caused by the cancer such as pain, obstruction, loss of appetite, fatigue, and jaundice. Additional support may also be required for psychosocial symptoms such as anxiety and depression.

Pain is well managed with oral analgesics such as Tylenol, codeine, morphine, oxycodone or fentanyl, depending on the severity of the pain[30]. Radiation is also often given to help relieve pain from locally advanced disease. Another effective approach in pain management is by nerve-block, where an anaesthetic or medication is injected to block or destroy the nerves[2].

In the case of obstruction, such as if the tumour is blocking the bile duct, a stents can be inserted using non-surgical approach such as ERCP or percutaneous transhepatic cholangiogram to relieve the blockage[2]. Biliary or gastric bypass surgery can also manage obstructive jaundice and gastric outlet obstruction. Managing anorexia-cachexia symptom is also very important for a patient's overall health and well-being and ultimately, survival. Special diets containing omega-3 fatty acid diets, and other supplements such as dexamethasone, magistrol or eicosopentanoic acid can help patients maintain or gain weight[32]. Finally, depression is also one of the most common symptoms associated with diagnosis of pancreatic cancer, where its treatment includes the prescription of anti-depressants, cognitive therapy, psychotherapy or the use of other alternative methods such as yoga, acupuncture or social groups. Depression is associated with fatigue and pain, thus the treatment of these symptoms can also help relieve depression[34]. As most of the above-mentioned symptoms are closely linked and related to one another, the effective management of all symptoms is essential for the overall improvement of a patient's quality of life and experience.

2.3. Patient Decision Aids

With the primary aim being to communicate knowledge about the treatment options available for a particular disease, in a way that facilitates the decision-making process, patient decision aids are becoming increasingly more important sources of information and decision guides for patient healthcare. Regardless of the disease and treatment options being presented, advantages and disadvantages exist for each treatment choice and patients often find themselves in the situation where they must weigh the different options against each other to arrive at a suitable treatment choice, which often depends on their individual preferences and values. Such complex decisions are referred to as preference-sensitive decisions, where the individual values and preferences of a patient may determine which treatment is best suited for them[35]. Without an information tool or decision

guide, such as a decision aid, patients may feel uncertain about the best course of action and may be at risk of pursuing a treatment option without completely understanding the benefits and risks of the treatment. In effort to resolve the decisional conflict that may be encountered by patients faced with these difficult decisions, patient decision aids have been developed and largely applied to clinical settings, especially the patient role in the choice of their treatment have become significantly greater.

2.3.1. Patient Decision Aid definition

Patient Decision aids are defined as tools that "communicate evidence on treatment options to patients in ways that encourage them to engage with their practitioners to choose an intervention that is consistent with the evidence and with their personal values"[36]. Another definition highlights the importance of patient decision aids in improving patient knowledge of options, while incorporating patient preferences and values, and increasing the patient's involvement in health decision-making[37]. Information in patient decision aids can be presented in booklets, pamphlets, videos or DVDS and other types of multimedia. The Internet is becoming a more popular format for decision aids as it makes it easy for physicians and researchers to update the tools as new evidence is published with minimal costs[38].

2.3.2. Application of Decision Aids

Decision aids have been shown to improve patient knowledge and perceived acceptability of an intervention such as chemotherapy, while diminishing decisional conflict[39]. Evidence for the clinical application of patient decision aids has been presented in a systematic review and meta-analysis conducted at the Ottawa Health Research Institute, which evaluates the effectiveness of patient decision aids[40]. An updated Cochrane review of 86 randomized control trials found that patient decision aids significantly improved decision quality as measured by the International Patient Decision Aids Collaboration (IPDAS) criteria[41].

Patient decision aids are often used in situations where decisions may be preference-sensitive or where the benefit-harm ratio is uncertain[40]. Thus, their use has recently been adopted in oncology,

where treatment options including choice between supportive care alone and chemotherapy can cause decisional conflict and uncertainty among patients. Although less decision aids are available in oncology settings, particularly for advanced cancers, the need for a patient decision aid is arguably even greater, as decisions are heavily based on preferences and values, which differ significantly across patients. Furthermore, cancer patients are seeking information about their treatment options and expressing that they wish to be active participants in the decision-making process[41]. Despite the fact that disease outcomes, prognosis and treatment options are discussed with the patient by the attending oncologist, the patients' understanding and retention of information about their diagnoses and about the risks and benefits of the available treatments remains unclear[42, 43]. Recent study findings on information retention in colorectal cancer patients who underwent surgery at The Ottawa Hospital emphasize the importance of the use of patient decision aids[42]. It was found that patients retain little from the informed consent discussions with their oncologist and require an aid to improve their overall knowledge. One third of patients with cancer misunderstand the information they receive at time of consultation[43]. Randomized trials suggest a role for patient decision aids in oncology to improve patient knowledge and information retention[44-48].

2.3.2.1. Application of decision aids in pancreatic cancer

Although patient decision aids have been used in the oncology setting for advanced breast cancer, prostate cancer, and most recently colorectal cancers, they have not yet been applied to the pancreatic cancer patient population.

Pancreatic cancer patients are very vulnerable and face many difficult decisions. Unfortunately, due to the majority of incoming patients being diagnosed at a later disease stage, and the need to start therapy as soon as possible to avoid further spread of the disease, patients are given little to no time to make their treatment decision. Thus, patients are often overloaded with information about their diagnosis, treatment options, side effects and survival statistics associated at their first consultation visit. Within the one-hour consultation, patients must digest this information and process it in order to make a choice. Therefore, the introduction of a decision aid to patients that is distributed prior to their consultation with the medical oncologist can significantly help reduce the burden that these complex

treatment decisions may impose and provide valuable information about the risks and benefits that each treatment option offers. It is hypothesized that the use of a decision aid will improve physician-patient communication and assist patients with pancreatic cancer in choosing between different treatment options. A decision aid will further help physicians better understand their patients' individual preferences and expectations in order to help guide them through their choice.

3. SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF CHEMOTHERAPY REGIMENS FOR ADVANCED PANCREATIC CANCER

3.1. Rationale:

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in North America. In the U.S. there will be 45 220 new cases in 2013, with 38 460 deaths due to pancreatic cancer[3]. Prognosis is poor with a five-year overall survival rate of 6% for all cases. Due to the insidious nature of the disease, 80-85% of patients will be diagnosed with advanced disease at presentation, where the five year overall survival rate drops to only 2%[1].

While supportive care measures such as opioids, radiotherapy and nerve blocks are critical for optimal symptom management in patients with advanced disease, systemic chemotherapy has had the greatest impact on survival. Since the approval of gemcitabine as the standard first-line therapy in 1997, several new systemic regimens have been developed to treat this population of patients. However, over this sixteen-year period, only modest improvements in survival outcomes have been observed[2]. The most recent published meta-analysis suggested modest additional survival benefits for gemcitabine-based doublet combination therapies[11]. Drugs combined with gemcitabine included oxaliplatin, capecitabine, cisplatin, irinotecan, exatecan, pemetrexed, axinitib, tipifarnib, marismastat, or 5-fluorouacil[14-19, 49-61] as well as gemcitabine based biologic therapies, erlotinib and more recently the combination of erlotinib and bevacizumab[20,24]. In 2005, a four-drug regimen, including gemcitabine, cisplatin, epirubicin, 5-fluourouacil (PEFG) demonstrated improved overall and progression free survival over gemcitabine alone[27]. In 2011, a four drug regimen known as FOLFIRINOX, which included folinic acid (FOL), 5-flourouacil (F), irinotecan (IRIN) and oxaliplatin (OX), was demonstrated to have clinically superior survival outcomes compared to gemcitabine alone[28]. This resulted in an increasing adoption of FOLFIRINOX as the treatment of choice for patients with good performance status (ECOG 0-1/KPS>70). However, there is controversy as to whether the survival benefits of four drug combination regimens outweigh the associated toxicities. Most recently, in

January 2013, a trial comparing gemcitabine plus nab-Paclitaxel versus gemcitabine alone demonstrated a statistically significant survival benefit for this new doublet, introducing this as a less complex two-drug option for the management of advanced pancreatic cancer[26]. With the introduction of these effective therapies, and the lack of large, high quality randomized trials that compare all eligible treatments, it was of interest to indirectly compare the relative efficacy and safety of these treatments in an objective manner using a network meta-analysis.

3.2. Objectives

The objective was to perform a comprehensive and inclusive systematic review of all phase III randomized clinical trials published over the last decade and then compare the relative efficacy and safety of these treatments using a Bayesian network meta-analysis. The network meta-analysis incorporates both direct and indirect comparisons, using gemcitabine as the reference comparator, in order to compute the hazard ratios for overall survival, progression free survival, overall response rates and safety outcomes between all treatments on a relative scale. This analysis also provides information about the rankings of various treatments in terms of survival outcomes and safety.

3.3. Methods

3.3.1. Search Strategy

Randomized studies in any language were searched using the Cochrane Central Registry of Controlled trials as well as Medline, PubMed and the clinical trials database of the National Cancer Institute from January 1st, 2002 until January 31st, 2013. The search strategy included the key words “advanced OR metastatic AND pancreatic cancer OR adenocarcinoma OR pancrea* OR malign* neoplasm” and was further screened in an advanced search for randomized clinical trials (Appendix 1). Abstract books and presentations of major meetings of the American Society of Clinical Oncology (ASCO) were also searched to identify any phase III trials that had not been picked up in the initial search or had not further been published as full-text articles. The inclusion of abstracts can further minimize possible publication bias where negative studies may not have been published as full-text articles.

3.3.2. Eligibility Criteria and Trial Selection

All randomized clinical trials with at least two arms comparing different chemotherapy regimens in patients with advanced pancreatic cancer between January 1st, 2002 and January 31st 2013 were considered. Clinical trials comparing chemotherapy either in the form of monotherapy or combination therapy were included if they were either directly or indirectly connected to the reference comparator gemcitabine (1000mg/m^2) and if they enrolled at least 50 patients per arm based on the recommendations from the literature[62]. The trial population included patients who were eligible for first-line therapy and who were diagnosed with metastatic disease. Metastatic disease was defined as any cancer that has spread to different tissues and organs of the body while advanced disease can also include locally advanced cancer that is deemed unresectable due to the location of the tumour or involvement of surrounding lymph nodes. Trials including over 50% of patients with locally advanced disease in their treatment arms were excluded from this study because treatment approaches may differ from those offered for metastatic cases. Furthermore, survival outcomes for patients with locally advanced disease are often better. Trials that compared radiation or combination chemoradiation therapy in one or both arms were also excluded to avoid clinical heterogeneity. Finally, trials that included patients with pancreatic malignancies other than adenocarcinoma such as neuroendocrine pancreatic cancers were excluded. Intervention of interest included any experimental form of single-agent or combination chemotherapy for advanced or metastatic pancreatic cancer where the comparators were head-to-head. Finally, outcomes of interest included overall survival, progression free survival and overall response rate and safety outcomes, which will be described in detail in section 3.2.3. Two authors (GG and DJ) independently screened the abstracts and selected eligible trials. Any discrepancies were discussed with a third author (SG).

3.3.3. Outcome measures

The main outcomes assessed in this study were overall and progression free survival. Overall survival was calculated from the date of randomization into the respective trial until the date of death or last follow-up. Progression-free survival was calculated from the date of randomization until the date of documentation of disease progression. Differences in the time-dependent survival outcomes were

computed as log hazard ratios within the network meta-analysis. Minor outcomes included overall response rate (ORR) and safety, and as dichotomous variables were assessed using odds ratios.

The ORR was calculated from the proportion of complete and partial responses as defined in the ERTCC v 3.0 and divided by the total number of patients per arm. Grade 3 (serious) or 4 (life-threatening) adverse events of interest were specified *a priori* and included febrile neutropenia, neutropenia, fatigue, vomiting, diarrhea and sensory neuropathy as defined in the Common Terminology Criteria in Adverse Events (CTCAE) v 3.0.

3.3.4. Data extraction

Trial data collected included the authors' names, the journal, year of publication, country of origin, number of participating centers, inclusion and exclusion criteria, stratification, major and minor endpoints, number of arms, sample size per arm, regimens used, doses and line of treatment. In addition, patient characteristics were also taken into account including the proportion of males, proportion of stage IV disease and proportions of good ECOG or KPS performance status, and survival outcomes. All data were extracted from the original primary studies except where there were multiple publications of a single randomized clinical trial, in which case, data from the most recent adjudicated publication was used in the analysis. Data extraction and entry was accomplished by a single reviewer (GG).

3.3.4.1. Quality assessment

The Scottish Intercollegiates Guidelines Network (SIGN) 50 assessment scale was used in order to determine the overall methodological quality of the studies[63]. A single reviewer assessed the overall quality and bias of selected studies (GG). A summary of responses for each trial can be found in Appendix 2. This was based on answers about sources of funding, internal validity and risk of bias. High quality studies (++), where the majority of SIGN 50 criteria were met, indicated little or no risk of bias and results were unlikely to be changed by further research. In acceptable quality (+) studies, most criteria were met, but flaws in the study could be associated with risk of bias and conclusions may

change in the light of further studies. In low quality studies (-) most criteria were not met and it presented significant flaws relating to key aspects of study design and conclusions were likely to change in the light of further studies[63].

3.3.5. Statistical Analysis

Descriptive statistics were generated for trial and study population characteristics across all eligible trials using SAS (9.2; Cary, NC). Median values were obtained for each characteristic per arm when applicable, and overall trial proportions were calculated from data provided in the trial's study characteristics.

3.3.5.1. Meta-analysis

Pairwise comparisons were generated by synthesizing studies that compared the same interventions into a random effects model. Random effects models were used for the pairwise comparison with the exception of the use of fixed effects models for comparisons in which only a single study was included for that particular treatment comparison. The pooled hazard ratios and 95% confidence intervals were then reported for each continuous outcome such as overall survival and progression free survival, and odds ratios and 95% confidence intervals were obtained in the comparison of side effects. All statistical analyses of the meta-analysis were conducted using RevMan[5.2, Cochrane Collaboration, Copenhagen][64].

3.3.5.2. Network meta-analysis

A Bayesian network meta-analysis was performed in order to simultaneously compare all treatments in the network. The network meta-analysis can be thought of as an extension of the traditional meta-analysis as it incorporates both direct and indirect information through a common comparator in order to obtain estimates of the relative treatment effects on the multiple treatment comparisons[65-68]. For instance, by obtaining information from a trial comparing drug A to B, and B to C, an indirect estimate

of the benefit of A over C can be achieved[67]. A normal likelihood model incorporating log hazard ratios of treatment differences was used for the analyses. Bayesian methods combine a prior probability distribution with a distribution of the pooled effect based on the observed data in order to obtain posterior probability distribution of the pooled effect[66, 68,69]. In other words, the prior belief of possible values for the pooled effect can be combined with the likelihood for these effects, where the likelihood provides information on the extent to which different values for the parameter of interest is supported by the data[70]. The resulting posterior distribution allows for its interpretation in terms of probabilities where the probability of a treatment resulting in a smaller or larger increase of survival can be determined. Furthermore, the posterior results are not influenced by the prior distribution because non informative prior distributions are being used prior to seeing the data, and thus, the posterior distribution is driven completely by the data[66]. The Bayesian framework for network meta-analyses also allows for the probabilistic interpretation of uncertainty and ranking of interventions[70]. Therefore, it makes it possible to identify the most effective treatment and to rank treatments in order of effectiveness and tolerability.

Gemcitabine (1000 mg/m^2), a long-time standard therapy for advanced pancreatic cancer, was selected as the reference comparator in the Bayesian network meta-analysis because it has consistently been used as the comparator in the majority of randomized clinical trials available for advanced pancreatic cancer. Following assessment of heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols, point estimates and 95% credible intervals were generated. Credible intervals represent the extent of uncertainty around the point estimate and thus can be interpreted as the probabilistic statement about the parameter. Absolute prolongation of survival with various regimens for a patient was calculated based on the median survival of gemcitabine, the standard therapy and reference comparator for the network meta-analysis. It was calculated as [(gemcitabine median OS/HR)*gemcitabine median OS].

The probability of a comparator being optimal was estimated for each outcome and the mean rank was calculated, by counting the proportion of iterations of the Markov chain in which each drug had the highest HR. Vague or flat priors, such as N (0, 100^2) were assigned for basic parameters throughout[71]. Outcomes were compared from the fixed and random effects models and reported estimates from the model with a better fit, which was based on the deviance information criterion and

comparing the residual deviance with the number of unconstrained data points. To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed. Three chains were fit in WinBUGS for each analysis, with at least 40,000 iterations, and a burn-in of at least 40,000 iterations[71]. All Bayesian network meta-analyses were conducted in WinBUGS 1.4 (MRC Biostatistics Unit, Cambridge, UK). A detailed description of the code and procedures followed to run the Bayesian network meta-analysis in WinBUGS is provided in Appendix 3.

3.3.5.3. Assessment of heterogeneity

Clinical heterogeneity was first assessed through clinical judgment with input from experts in the field. Statistical heterogeneity was then assessed by visually inspecting forest plots from pairwise analysis to determine whether there was overlap in the confidence intervals, as this would suggest heterogeneity. A formal assessment of heterogeneity was then accomplished by referring to the I^2 statistic. Following standard guidelines, I^2 values greater than 50% are considered high heterogeneity levels, between 25-50% moderate and less than 25% considered low heterogeneity levels. In instances where heterogeneity was suspected, sensitivity analysis was employed.

3.3.5.4. Sensitivity analysis

Sensitivity analyses were then employed to adjust for important covariates based the suspicion of heterogeneity from either the clinical or statistical assessments of heterogeneity, as described in the previous sections. Sensitivity analysis or meta-regression would only be performed for major outcomes if significant heterogeneity (I^2 value greater than 50%) were observed.

3.3.5.5. Subgroup analysis

Covariates were selected *a priori* for subgroup analysis based on clinical recommendations. Subgroups analyzed in the Bayesian network meta-analysis included patient performance status, trial sample size and the proportion of stage IV disease versus locally advanced. The sensitivity analysis for patient

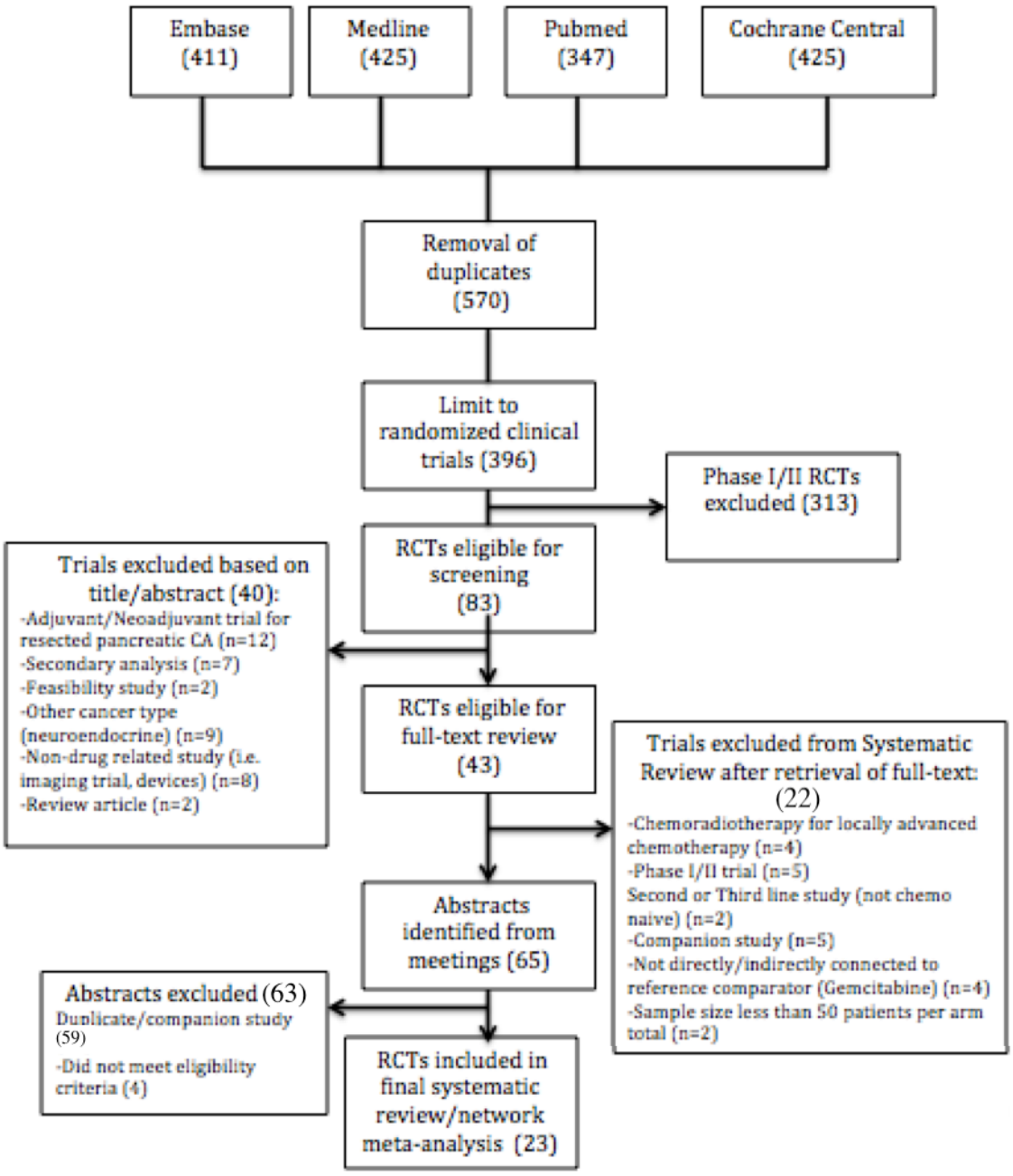
performance status excluded trials with a proportion of patients with greater than 85% ECOG PS 0-1/KPS of 90-100, based on clinical recommendations. The sensitivity analysis for trial size utilized a threshold value of 100 patients/arm, based on recommendations from Juni et al[68]. The sensitivity analysis for stage mix (locally advanced versus metastatic) excluded trials with 80% or fewer of patients with stage 4 disease.

3.4. Results

3.4.1. Trial Selection

The initial search of the population resulted in 1747 studies (Figure 1). After removal of duplications and search limits to 2002-2013 and phase III randomized clinical trials, 83 trials were eligible for screening. Exclusion based on abstract/titles was accomplished for 40 trials. The remaining 43 trials were screened based on full-text where 22 trials were excluded based on wrong diagnosis (n=4), phase I/II trial (n=5), cross over trial design (n=2), companion study (*ie.* interim analysis, sensitivity analysis, *etc.*) (n=5), not directly or indirectly connected to gemcitabine (n=4), inadequate quality (n=2)(Figure 1). Figure 1). A search of major scientific meetings was also performed to identify abstracts that were not published as full-text articles. This search yielded an additional 2 abstracts to include in the systematic review and network meta-analysis.

Figure 1: CONSORT diagram of search strategy and results for randomized controlled clinical trials evaluating treatments for advanced pancreatic cancer



3.4.2. Characteristics of included trials

Characteristics of the included trials are outlined in Table 1. A total of 9989 randomized patients were included in the analysis. The majority of the trials had two arms and compared gemcitabine to an experimental treatment. Individual trial arms were evenly distributed between age, gender and performance status. Using the SIGN 50 scale, 5/23 studies (21.7%) were reported as high quality and the remaining 18 studies (78.3%) as acceptable quality studies. For the primary outcomes of interest, nineteen unique comparisons were available for 23 different trials. The resulting network geometry is depicted in Figure 2.

Table 2: Characteristics of eligible randomized clinical trials included in the network meta-analysis

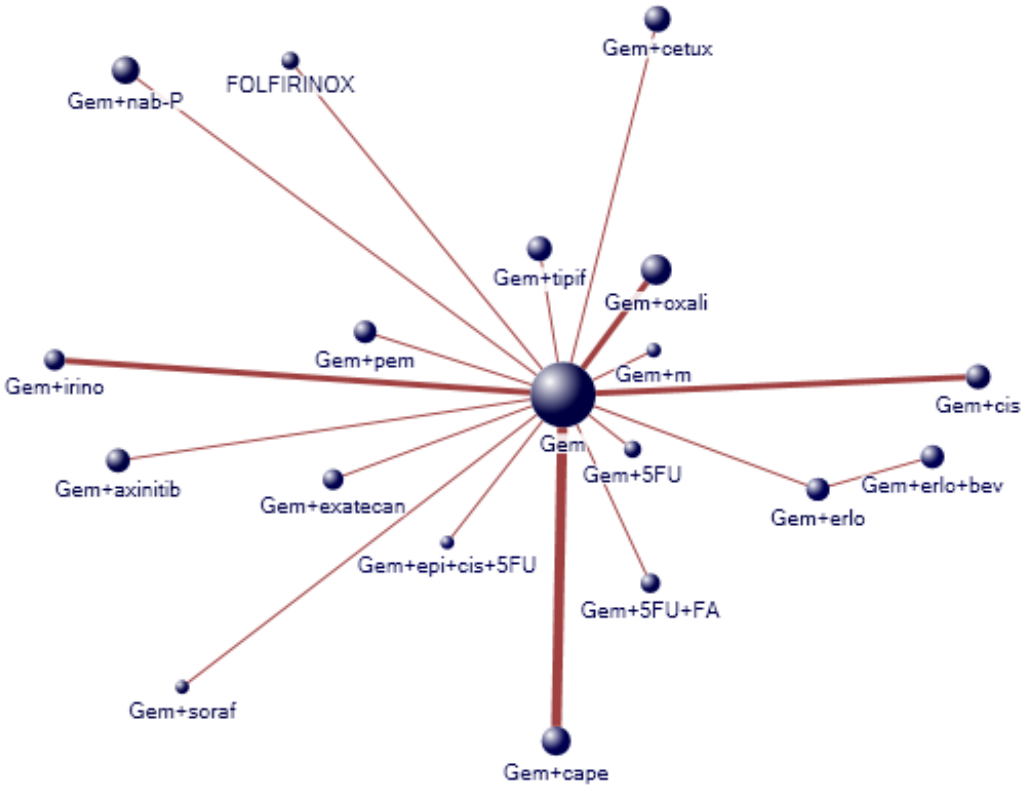
Study: Author (year)	Study design: Number of patients per arm	Regimens: Arm 1	Regimens: Arm 2	Outcomes	Publication type	Quality (Sign50)
Bramhall (2002)	RCT-double blinded N1=119 N2=120	Gemcitabine (1000 mg/m^2)	Gemcitabine +Marismastat	OS PFS ORR	Full-text	++
Berlin (2002)	RCT-single blinded N1=162 N2=160	Gemcitabine (1000 mg/m^2)	Gemcitabine+5FU	OS PFS ORR	Full-text	+
VanCustem (2004)	RCT- double blinded N1=344 N2=344	Gemcitabine (1000 mg/m^2)	Gemcitabine +Tipifarnib	OS PFS ORR	Full-text	++
Rocha Lima (2004)	RCT- single blinded N1=180 N2=180	Gemcitabine (1000 mg/m^2)	Gemcitabine +Irinotecan	OS ORR	Full-text	+
Louvet	RCT- single blinded	Gemcitabine	Gemcitabine	OS	Full-text	+

(2005)	N1=156 N2=157	(1000 mg/m^2)	+Exatecan	PFS ORR		
Reni (2005)	RCT- single blinded N1=47 N2=52	Gemcitabine (1000 mg/m^2)	Gemcitabine + Oxaliplatin	OS PFS ORR	Full-text	+
Riess (2005)	RCT- single blinded N1=238 N2=235	Gemcitabine (1000 mg/m^2)	Gemcitabine +epirubicin +cisplatin+5FU	OS PFS ORR	Abstract	+
Herrmann (2007)	RCT- single blinded N1=159 N2=160	Gemcitabine (1000 mg/m^2)	Gemcitabine+5FU +folinic acid	OS PFS ORR	Full-text	+
Oettle (2005)	RCT- single blinded N1=282 N2=283	Gemcitabine (1000 mg/m^2)	Gem+ Capecitabine	OS PFS ORR	Full-text	+
Abou-Alfa (2006)	RCT- single blinded N1=175 N2=1175	Gemcitabine (1000 mg/m^2)	Gem+Pemetrexed	OS ORR	Full-text	+
Heinemann (2006)	RCT- single blinded N1=97 N2=98	Gemcitabine (1000 mg/m^2)	Gemcitabine +Cisplatin	OS PFS ORR	Full-text	+
Stathopoulos (2006)	RCT- single blinded N1=70 N2=60	Gemcitabine (1000 mg/m^2)	Gemcitabine +Irinotecan	OS ORR	Full-text	+

Poplin (2006)	RCT- single blinded N1=275 N2=272	Gemcitabine (1000 mg/m^2)	Gemcitabine + Oxaliplatin	OS PFS ORR	Full-text	+
Moore (2007)	20 RCT- double blinded N1=285 N2=284	Gemcitabine (1000 mg/m^2)	Gemcitabine +Erlotinib	OS PFS ORR	Full-text	++
Cunningham (2009)	RCT- single blinded N1=266 N2=267	Gemcitabine (1000 mg/m^2)	Gem + Capecitabine	OS PFS ORR	Full-text	+
VanCustem (2009)	RCT- Double blinded N1=301 N2=306	Gemcitabine + Erlotinib	Gem+Erlotinib+ Bevacizumab	OS PFS ORR	Full-text	++
Philip (2010)	RCT- single blinded N1=371 N2=372	Gemcitabine (1000 mg/m^2)	Gemcitabine + Cetuximab	OS PFS ORR	Full-text	++
Colucci (2010)	RCT- single blinded N1=199 N2=201	Gemcitabine (1000 mg/m^2)	Gem+Cisplatin	OS PFS ORR	Full-text	+
Kindler (2011)	RCT-Double blinded N1=315 N2=180	Gemcitabine (1000 mg/m^2)	Gem+Axinitib	OS PFS ORR	Full-text	++
Conroy (2011)	RCT- single blinded N1=171 N2=171	Gemcitabine (1000 mg/m^2)	FOLFIRINOX	OS PFS ORR	Full-text	+

Goncalves (2012)	RCT- double blinded N1=52 N2=52	Gemcitabine (1000 mg/m^2)	Gem+Sorafenib	OS PFS ORR	Full-text	++
Heinemann (2012)	RCT-single blinded N1=143 N2=131	Gemcitabine + Erlotinib	Capecitabine+ Erlotinib	OS PFS ORR	Full-text	+
Von Hoff (2013)	RCT- single blinded N1=430 N2=431	Gemcitabine (1000 mg/m^2)	Gem+ NAB-Paclitaxel	OS PFS ORR	Abstract	+

Figure 2: Network of eligible comparisons for the network meta-analysis



Circle size is proportionate to the number of patients, thickness of line represents number of trials per comparison and distance of circle to reference comparator (gemcitabine) is proportionate to year of publication where 1cm=2 years.

Gem=gemcitabine. 5FU=5-fluorouacil. FA=Folinic Acid. Erlo=erlotinib. Epi=epirubicin. Bev=bevacizumab. Cape=capecitabine. Soraf=sorafinib. M=marismastat. Cis=cisplatin. Irino=irinotecan. Oxali=oxaliplatin. Tipif=tipifarnib. Cetux=cetuximab. Nab-P=nab-paclitaxel.

3.4.3. Individual Study results

A summary of the weighted hazard ratios and 95% confidence intervals for major outcomes are included in Table 3. Pairwise comparisons were accomplished for 19 unique comparisons. The weighted hazard ratios for the primary outcome, overall survival, were calculated for each comparison. Statistical heterogeneity was assessed using the i^2 statistic, which was low (<1%) across all trials indicating good balance between treatment arms. The forest plot including each of the pairwise comparisons can be found in Appendix 4. Due to the low heterogeneity across trials, all studies included in the systematic review and meta-analysis were analyzed in the network meta-analysis.

Table 3: Pairwise comparisons of various treatments for advanced pancreatic cancer

Comparator	*No. of studies*	*Total no. of patients*	*HR (95% CI)*	*I^2(%)*
FOLFIRINOX	*1*	*342*	*0.57 (0.45-0.73)*	*NA*
Gemcitabine + 5-fluorouacil	*1*	*322*	*0.82 (0.65-1.03)*	*NA*
Gemcitabine + 5-flourouacil+folinic acid	*1*	*473*	*1.04 (0.86-1.25)*	*NA*
Gemcitabine + axinitib	*1*	*632*	*1.01 (0.79-1.31)*	*NA*
Gemcitabine + capecitabine	*2*	*852*	*0.82 (0.71-0.94)*	*0*
Gemcitabine + cisplatin	*3*	*678*	*1.02 (0.89-1.17)*	*0*
Gemcitabine + cetuximab	*1*	*766*	*1.06 (0.91-1.23)*	*NA*
Gemcitabine + epirubicin + cisplatin +5FU	*1*	*104*	*0.65 (0.43-0.99)*	*NA*
Gemcitabine + erlotinib	*1*	*569*	*0.82 (0.68-0.98)*	*NA*
Gemcitabine + exatecan	*1*	*349*	*0.98 (0.81-1.19)*	*NA*
Gemcitabine + irinotecan	*1*	*360*	*1.04 (0.84-1.29)*	*NA*

Gemcitabine + marismastat	*1*	*239*	*0.99 (0.76-1.29)*	*NA*
Gemcitabine + nab-paclitaxel	*1*	*861*	*0.72 (0.62-0.84)*	*NA*
Gemcitabine + pemetrexed	*1*	*565*	*0.98 (0.82-1.18)*	*NA*
Gemcitabine + sorafenib	*1*	*104*	*1.27 (0.84-1.93)*	*NA*
Gemcitabine + tipifarnib	*1*	*688*	*0.97 (0.81-1.16)*	*NA*

*. ** Hazard Ratios not reported. A hazard ratio greater than 1 indicates that gemcitabine has better survival. NA=not applicable (only 1 study available for that comparison)*

3.4.4. Network Meta-Analysis

The effect estimates from both the fixed and random-effects models were comparable and matched closely to the estimates derived from the pairwise comparisons in both direction and magnitude.

3.4.4.1. Major outcomes

For overall survival, FOLFIRINOX, PEFG, gemcitabine+NAB-Paclitaxel, gemcitabine+erlotinib with or without bevacizumab, gemcitabine+capecitabine, and gemcitabine+oxaliplatin were associated with statistically significant hazard ratios relative to gemcitabine alone (Figure 3).

Treatments that were associated with statistically significant survival benefits over gemcitabine alone as well as other combination therapies analysed in the network meta-analysis were: FOLFIRINOX; PEFG; gemcitabine+NAB-P; gemcitabine+erlotinib+bevacizumab; gemcitabine+erlotinib; gemcitabine+capecitabine and gemcitabine+oxaliplatin (Figure 3). No other combination therapies included in this network meta-analysis were found to have statistically significant hazard ratios in comparison to the other treatments.

FOLFIRINOX was associated with statistically significant hazard ratios relative to fifteen different treatments including gemcitabine alone, gemcitabine+oxaliplatin, gemcitabine+capecitabine, gemcitabine+cisplatin, gemcitabine+5-fluorouacil, gemcitabine+5-fluorouacil/folinic acid, gemcitabine+pemetrexed, gemcitabine+irinotecan, gemcitabine+exatecan, gemcitabine+axinitib, gemcitabine+tipifarnib, gemcitabine+ marimastat and gemcitabine+sorafenib (Figure 3). There was an

OS gain of 4.2 months (95% Cl 2.2-6.9) over gemcitabine alone (Table 2). FOLFIRINOX had a median survival advantage of 4 months (range 0.8-6.9 months) over all treatments included in the analysis (Table 2). FOLFIRINOX was calculated to have a 64.9% probability of being best for OS (Figure 4). Using the mean rank scale, FOLFIRINOX was ranked first with a mean rank of 1.5 out of 20 treatments (Figure 5). FOLFIRINOX was not associated with statistically significant hazard ratios for OS compared to gemcitabine plus NAB-paclitaxel [hazard ratio (HR) 0.79 (0.59-1.05)], PEFG (epirubicin, cisplatin, 5FU plus gemcitabine [HR 0.88 (0.54-1.43)], or the combination of gemcitabine, erlotinib plus bevicizumab [HR 0.78, (0.55-1.11)]. FOLFIRINOX was associated with statistically significant hazard ratios for PFS in thirteen treatment regimens (Table 2). It had a 63.1% probability of being best and had a mean rank of 1.38 for PFS. FOLFIRINOX was ranked first for PFS and was associated with statistically significant hazard ratios relative to other regimens, excluding gemcitabine+ NAB paclitaxel, Gemcitabine+erlotinib+bevacizumab, gemcitabine+pemetrexed, gemcitabine+irinotecan and PEFG (Table 2).

PEFG was ranked second for OS and PFS with a hazard ratio of 0.65, 95% CI 0.43-0.98, and median survival gain of 3 months (95% CI 0.1-7 months) over gemcitabine alone. It was calculated to have a mean rank of 3.4 out of 20 treatments for OS (Figure 5). It was associated with statistically superior hazard ratios over gemcitabine+cetuximab, gemcitabine+irinotecan, gemcitabine +5FU/FA, and gemcitabine+sorafenib (Figure 3).

Gemcitabine plus NAB+paclitaxel was ranked third for OS (Mean Rank 3.8/20) (Figure 5). It was associated with a statistically significant benefit in survival over gemcitabine alone (HR: 0.72,95% CI 0.62-0.82), gemcitabine+cisplatin (HR: 0.73 95% CI 0.59-0.91), gemcitabine+5FU/FA (HR: 0.69 95% CI 0.54-0.88), gemcitabine+pemetrexed (HR: 0.73 95% Cl 0.58-0.93), gemcitabine+exatecan (HR: 0.73 95% CI 0.57-0.94), gemcitabine+cetuximab (HR: 0.68, 95%CI 0.55-0.84) and gemcitabine+sorafenib (HR 0.56 95% CI 0.36-0.88) (Figure 3). Gemcitabine+NAB-paclitaxel had a median increase of OS time of 2.2 months (95% CI 1.1-3.4) over gemcitabine alone and an overall mean of 2 months (95% CI -0.5-4.3 months) over the other treatments included. It was associated with statistically significant hazard ratios for PFS in comparison to gemcitabine alone and gemcitabine+cisplatin.

The combination of gemcitabine, erlotinib and bevacizumab was ranked fourth for overall survival, with a mean rank of 4.3. It was associated with statistically significant survival benefit over gemcitabine alone with a survival gain of 2.1 months (95% CI 0.34-4.4 months), as well as gemcitabine+irinotecan, gemcitabine+sorafenib, gemcitabine+5FU/FA and gemcitabine+cetuximab (Figure 3).

Gemcitabine plus erlotinib (without bevacizumab) was also found to be associated with a statistically significant survival benefit over gemcitabine alone (survival gain 1.2 months, 95% CI 0.11-2.57) and over gemcitabine plus cetuximab (Figure 3).

Gemcitabine plus capecitabine had statistically longer survival than gemcitabine alone, gemcitabine+sorafenib, gemcitabine+5FU/FA, and gemcitabine+cetuximab. It was associated with statistically worse overall survival compared to FOLFIRINOX (HR 1.43, 95% CI 1.09-1.89).

In this multi-treatment comparison, the combination of gemcitabine and sorafenib was associated with statistically significant worse survival outcomes in comparison to FOLFIRINOX, PEFG, Gem+erlotinib+bev, Gem+erlotinib, and Gem+Oxaliplatin. It was ranked last for OS and PFS with a mean rank of 18.2 of 20 treatments and 12.14 out of 15 treatments, respectively.

Table 4: Indirect comparisons of available treatments for advanced pancreatic cancer

Indirect Comparison	**Overall Survival** HR (95% CI)	**Survival gain over OS*** Months (95% CI)	**Progression Free Survival** HR (95% CI)	**Progression Free survival gain** Months (95% CI)
FOLFIRINOX vs.				
Gemcitabine	0.57 (0.45-0.72)*	4.22 (2.12-6.92)*	0.59 (0.37-0.47)*	3.73 (0.98-6.48)*
Gemcitabine+ Nab-P	0.79 (0.59-1.05)	1.46 (-0.27-3.81)	0.68 (0.51-0.91)*	1.54 (0.32-3.16)*
Gemcitabine+Oxaliplatin	0.66 (0.50-0.88)*	2.83 (0.76-5.59)*	0.60 (0.43-0.85)*	2.17 (0.58-4.43)*
Gemcitabine+Capecitabine	0.70 (0.53-0.92)*	2.42 (0.48-5.0)	0.58 (0.45-0.74)*	2.40 (1.14-4.01)*
Gemcitabine+Cisplatin	0.58 (0.43-0.78)*	4.06 (1.62-7.3)	0.46 (0.34-0.62)*	3.94 (2.03-6.53)*
Gemcitabine +5FU	0.70 (0.49-0.97)*	2.45 (0.17-5.63)*	0.61 (0.44-0.84)*	2.11 (0.63-4.14)*
Gemcitabine+5FU/FA	0.55 (0.40-0.74)*	4.62 (1.93-8.28)*	n/a	n/a
Gemcitabine+pemetrexed	0.58 (0.43-0.74)*	4.03 (1.51-7.41)*	n/a	n/a
Gemcitabine+ irinotecan	0.55 (0.39-0.76)*	4.62 (1.76-8.54)*	n/a	n/a

Gemcitabine+epirubicin+cisplatin+ 5FU	0.88 (0.54-1.43)	0.80 (-1.66-4.76)	0.92 (0.57-1.48)	0.28 (-1.07-2.47)
Gemcitabine+exatecan	0.58 (0.43-0.79)*	4.03 (1.44-7.53)*	n/a	n/a
Gemcitabine+erlotinib	0.70 (0.51-0.94)*	3.94 (1.47-3.94)*	0.61 (0.45-0.82)*	2.11 (0.72-3.96)*
Gemcitabine+erlotinib+ bevacizumab	0.78 (0.55-1.11)	1.57 (-0.55-4.61)	0.63 (0.45-0.88)*	1.95 (0.44-4.08)*
Gemcitabine+ axinitib	0.56 (0.40-0.80)*	4.36 (1.40-8.54)*	0.47 (0.33-0.66)*	3.76 (1.70-6.68)*
Gemcitabine+tipifarnib	0.59 (0.44-0.79)*	3.94 (1.47-7.27)*	0.64 (0.48-0.86)*	1.82 (0.54-3.54)*
Gemcitabine+marismastat	0.58 (0.40-0.83)*	4.13 (1.18-8.38)*	0.49 (0.35-0.70)*	3.37 (1.41-6.15)*
Gemcitabine+Sorafenib	0.45 (0.28-0.73)*	6.89 (2.11-14.6)*	0.45 (0.28-0.72)*	4.00 (1.30-8.32)*
Gemcitabine+Cetuximab	0.54 (0.40-0.71)*	4.82 (2.24-8.25)*	0.44 (0.33-0.58)*	4.21 (2.41-6.56)*

**p<0.05, n/a=comparison not available*

Figure 3: Hazard Ratios and 95% credible intervals for overall survival in indirect treatment comparisons from Bayesian network meta-analysis

Gem	**1.76 (1.38-2.24)***	**1.39 (1.19-1.62)***	**1.34 (1.01-2.34*)**	**1.17 (1.01-1.35)***	**1.22 (1.07-1.41)***	1.22 (0.97-1.53)	0.96 (0.80-1.16)	1.02 (0.85-1.22)	0.96 (0.77-1.20)	1.02 (0.84-1.24)	1.02 (0.87-1.19)	**1.22 (1.02-1.46)***	**1.37 (1.06-1.77)***	1.19 (0.88-1.63)	1.01 (0.77-1.32)	1.03 (0.86-1.23)	0.78 (0.52-1.20)	0.94 (0.81-1.10)	0.99 (0.76-1.27)
0.57 (0.73-0.45)*	FOLFIRINOX	0.79 (0.59-1.05)	0.88 (0.54-1.43)	**0.66 (0.50-0.88*)**	**0.70 (0.53-0.92)***	**0.69 (0.50-0.97)***	**0.55 (0.40-0.74)***	**0.58 (0.43-0.79)***	**0.55 (0.39-0.76)***	**0.58 (0.43-0.79*)**	**0.58 (0.43-0.80)***	**0.69 (0.51-0.94)***	0.78 (0.55-1.11)	0.68 (0.46-1.00)	**0.57 (0.40-0.82)***	**0.59 (0.43-0.79)***	**0.45 (0.28-0.73)***	**0.54 (0.40-0.71)***	**0.56 (0.40-0.80)***
0.84 (0.62-0.72)*	1.26 (0.95-1.68)	G+NAB-P	1.11 (0.71-1.73)	0.84 (0.68-1.04)	0.88 (0.72-1.08)	0.88 (0.67-1.16)	**0.69 (0.54-0.88)***	**0.73 (0.58-0.93)***	**0.69 (0.53-0.90)***	**0.73 (0.57-0.94)***	**0.73 (0.59-0.91)***	0.88 (0.69-1.11)	0.98 (0.73-1.33)	0.86 (0.61-1.22)	**0.73 (0.53-0.99)***	**0.74 (0.53-0.99)***	**0.74 (0.53-0.99)***	**0.68 (0.55-0.84)***	**0.71 (0.53-0.96)***
0.65 (0.43-0.98)*	1.14 (0.70-1.85)	0.90 (0.58-1.41)	G+epi+cis+5FU	0.76 (0.49-1.18)	0.80 (0.51-1.23)	0.79 (0.49-1.28)	**0.62 (0.39-0.98)***	0.66 (0.42-1.04)	0.63 (0.39-1.00)	0.66 (0.42-1.05)	0.66 (0.42-1.03)	0.79 (0.50-1.25)	0.89 (0.55-1.45)	0.78 (0.46-1.31)	0.65 (0.40-1.08)	0.67 (0.43-1.05)	**0.51 (0.28-0.92)***	**0.57 (0.40-0.82)***	0.64 (0.39-1.04)
0.86 (0.74-0.99)*	**1.51 (1.13-1.99*)**	1.19 (0.97-1.47)	1.32 (0.85-2.05)	G+oxali	1.05 (0.86-1.29)	1.11 (0.71-1.73)	0.83 (0.65-1.04)	0.88 (0.69-1.10)	0.83 (0.63-1.07)	0.88 (0.69-1.12)	0.87 (0.70-1.09)	1.05 (0.83-1.32)	1.18 (0.88-1.58)	1.03 (0.73-1.45)	0.87 (0.64-1.18)	0.88 (0.70-1.11)	0.68 (0.43-1.05)	**0.81 (0.66-0.99)***	0.85 (0.63-1.14)
0.98 (0.84-1.15)	**1.43 (1.09-1.89*)**	1.13 (0.92-1.39)	1.26 (0.81-1.95)	0.95 (0.78-1.17)	G+Cape	0.99 (0.76-1.30)	**0.78 (0.62-0.99)***	0.83 (0.66-1.05)	0.78 (0.61-1.02)	0.83 (0.66-1.06)	0.83 (0.67-1.03)	0.99 (0.79-1.25)	1.12 (0.84-1.50)	0.98 (0.70-1.37)	0.82 (0.61-1.12)	0.84 (0.67-1.06)	**0.64 (0.41-0.99)***	**0.77 (0.63-0.95)***	0.81 (0.60-1.08)
0.82 (0.65-1.03)	**1.44 (1.03-2.00*)**	1.14 (0.86-1.50)	1.26 (0.78-2.03)	0.96 (0.73-1.26)	1.00 (0.77-1.31)	G+5FU	0.78 (0.58-1.06)	0.84 (0.63-1.12)	0.79 (0.57-1.08)	0.84 (0.62-1.13)	0.83 (0.67-1.03)	0.99 (0.75-1.34)	1.12 (0.79-1.59)	0.98 (0.67-1.44)	0.83 (0.58-1.18)	0.84 (0.63-1.13)	0.64 (0.40-1.04)	0.77 (0.59-1.02)	0.81 (0.57-1.14)
1.04 (0.86-1.25)	**1.82 (1.34-2.47*)**	**1.44 (1.13-1.84)***	**1.60 (1.01-2.53)***	1.21 (0.93-1.58)	**1.27 (1.01-1.61)***	1.27 (0.94-1.71)	G+5FU+FA	1.06 (0.82-1.38)	1.00 (0.75-1.33)	1.06 (0.81-1.39)	1.06 (0.80-1.39)	1.27 (0.98-1.64)	**1.43 (1.04-1.96)***	1.24 (0.87-1.79)	1.05 (0.76-1.41	1.07 (0.83-1.39)	0.82 (0.52-1.30)	0.98 (0.77-1.25)	1.02 (0.74-1.41)
0.98 (0.82-1.18)	**1.72 (1.27-2.32*)**	**1.36 (1.07-1.83)***	1.06 (0.82-1.38)	1.14 (0.90-1.44)	1.20 (0.95-1.51)	1.19 (0.89-1.60)	0.94 (0.73-1.22)	G+pem	0.94 (0.71-1.25)	0.99 (0.77-1.30)	0.99 (0.77-1.28)	1.19 (0.92-1.54)	1.34 (0.98-1.84)	1.17 (0.82-1.68)	0.99 (0.71-1.37)	1.01 (0.78-1.30)	0.77 (0.49-1.22)	0.92 (0.73-1.17)	0.97 (0.71-1.32)
1.04 (0.84-1.29)	**1.82 (1.32-2.52*)**	**1.44 (1.10-1.88)***	1.60 (0.99-2.56)	1.21 (0.93-1.58)	1.27 (0.98-1.65)	1.27 (0.92-1.74)	1.00 (0.75-1.33)	1.06 (0.80-1.41)	G+Irino	1.06 (0.79-1.42)	1.06 (0.80-1.24)	1.27 (0.95-1.68)	**1.42 (1.02-1.99)***	1.24 (0.85-1.82)	1.05 (0.74-1.48)	1.07 (0.81-1.42)	0.82 (0.51-1.31)	0.98 (0.75-1.28)	1.03 (0.73-1.43)
1.04 (0.86-1.25)	**1.72 (1.01-2.34*)**	**1.36 (1.06-174)***	1.51 (0.95-2.39)	1.14 (0.89-1.46)	0.83 (0.66-1.06)	1.19 (0.88-1.62)	0.94 (0.72-1.23)	1.00 (0.77-1.30)	0.94 (0.70-1.26)	G+exatecan	0.99 (0.78-1.28)	1.19 (0.92-1.33)	1.34 (0.97-1.85)	1.17 (0.81-1.69)	0.98 (0.71-1.38)	1.01 (0.77-1.31)	0.77 (0.49-1.23)	0.92 (0.72-1.18)	0.97 (0.70-1.33)
0.98 (0.84-1.15)	**1.73 (1.29-2.30*)**	**1.36 (1.09-1.70)***	1.51 (0.97-2.38)	1.14 (0.82-1.42)	1.20 (0.97-1.49)	1.20 (0.97-1.49)	0.94 (0.74-1.21)	1.00 (0.79-1.28)	0.94 (0.72-1.24)	1.00 (0.79-1.29)	G+Cis	1.20 (0.94-1.53)	1.35 (0.99-1.83)	1.18 (0.83-1.67)	0.99 (0.73-1.36)	1.01 (0.80-1.29)	0.77 (0.50-1.21)	0.93 (0.74-1.15)	0.97 (0.71-1.31)
0.82 (0.68-0.98)*	**1.43 (1.07-1.95*)**	1.14 (0.90-1.44)	1.26 (0.80-1.99)	0.96 (0.73-1.26)	1.00 (0.80-1.26)	1.00 (0.74-1.34)	0.79 (0.61-1.02)	0.84 (0.65-1.08)	0.79 (0.59-1.05)	0.84 (0.64-1.09)	0.83 (0.63-1.10)	G+erlo	1.12 (0.94-1.35)	0.98 (0.76-1.26)	0.82 (0.60-1.14)	0.84 (0.66-1.09)	0.65 (0.41-1.02)	**0.77 (0.61-0.98)***	0.81 (0.59-1.11)
0.73 (0.56-0.94)*	1.28 (0.90-1.82)	1.01 (0.75-1.36)	1.12 (0.69-1.83)	0.85 (0.63-1.14)	0.89 (0.67-1.20)	0.89 (0.63-1.26)	**0.70 (0.51-0.97)***	0.74 (0.54-1.02)	**0.70 (0.50-0.98)***	0.74 (0.54-1.03)	0.74 (0.55-1.00)	0.89 (0.74-1.07)	G+erlo+bev	0.87 (0.64-1.19)	0.74 (0.51-1.07)	0.75 (0.55-1.03)	**0.57 (0.35-1.94)***	**0.69 (0.51-0.93)***	0.72 (0.50-1.03)
0.84 (0.61-1.14)	1.47 (0.99-2.17)	1.16 (0.82-1.64)	1.29 (0.76-2.16)	0.97 (0.69-1.37)	1.02 (0.73-1.44)	1.02 (0.69-1.50)	0.80 (0.56-1.15)	0.85 (0.60-1.22)	0.80 (0.55-1.17)	0.85 (0.59-1.23)	0.85 (0.60-1.21)	1.02 (0.79-1.31)	1.15 (0.84-1.56)	Cape+erlo	0.84 (0.56-1.27)	0.86 (0.60-1.23)	0.66 (0.39-1.11)	0.79 (0.55-1.11)	0.82 (0.55-1.23)
0.99 (0.76-1.30)	**1.74 (1.21-2.48)***	**1.37 (1.00-1.87)***	1.52 (0.93-2.49)	1.15 (0.85-1.57)	1.21 (0.90-1.64)	1.21 (0.85-1.72)	0.95 (0.69-1.32)	1.01 (0.73-1.40)	0.95 (0.67-1.35)	1.01 (0.73-1.41)	1.00 (0.74-1.38)	1.21 (0.87-1.67)	1.36 (0.93-1.97)	1.18 (0.79-1.79)	G+marisma	1.02 (0.74-1.41)	0.78 (0.48-1.29)	0.93 (0.69-1.27)	0.98 (0.67-1.42)
0.97 (0.81-1.16)	**1.70 (1.26-2.30)***	**1.35 (1.07-1.70)***	1.49 (0.95-2.35)	1.13 (0.90-1.43)	1.19 (0.95-1.49)	1.17 (0.86-1.59)	1.06 (0.82-1.38)	0.99 (0.77-1.28)	0.93 (0.70-1.24)	0.99 (0.76-1.29)	0.99 (0.78-1.25)	1.18 (0.92-1.52)	1.33 (0.97-1.82)	1.16 (0.81-1.66)	0.98 (0.71-1.36)	G+tipif	0.76 (0.48-1.20)	0.92 (0.72-1.16)	0.96 (0.70-1.31)
1.27 (0.83-1.93)	**2.22 (1.38-3.61)***	**1.76 (1.13-2.75)***	**1.95 (1.08-3.52)***	1.48 (0.95-2.31)	**1.56 (1.00-2.41)***	1.55 (0.96-2.50)	1.22 (0.77-1.93)	1.29 (0.82-2.04)	1.22 (0.76-1.96)	1.30 (0.82-2.06)	1.29 (0.82-2.01)	1.55 (0.98-2.44)	**1.74 (1.07-2.84)***	1.52 (0.90-2.56)	1.28 (0.78-2.11)	1.31 (0.83-2.07)	G+Soraf	1.20 (0.77-1.87)	1.25 (0.77-2.05)
1.06 (0.91-1.23)	**1.86 (1.40-2.47)***	**1.47 (1.19-1.82)***	**1.63 (1.05-2.53)***	**1.23 (1.00-1.53)***	**1.30 (1.06-1.59)***	1.29 (0.98-1.70)	1.02 (0.80-1.30)	1.08 (0.85-1.37)	1.02 (0.78-1.33)	1.08 (0.84-1.38)	1.08 (0.87-1.34)	**1.29 (1.02-1.63)***	**1.45 (1.08-1.96)***	1.27 (0.90-1.79)	1.07 (0.79-1.46)	1.09 (0.87-1.38)	1.20 (0.77-1.87)	G+Cetux	1.04 (0.78-1.41)
0.96 (0.78-1.18)	**1.78 (1.25-2.52)***	**1.41 (1.04-1.89)***	1.56 (0.96-2.55)	1.18 (0.88-1.59)	1.24 (0.93-1.66)	1.24 (0.88-1.74)	0.97 (0.71-1.34)	1.04 (0.76-1.42)	0.98 (0.70-1.37)	1.04 (0.75-1.43)	1.03 (0.76-1.39)	1.23 (0.90-1.69)	1.39 (0.97-2.00)	1.21 (0.81-1.81)	1.02 (0.71-1.49)	1.04 (0.77-1.43)	0.80 (0.49-1.30)	0.96 (0.71-1.29)	G+axinitib

Figure 4: Probability of a treatment being best of 100% for overall survival and progression free survival

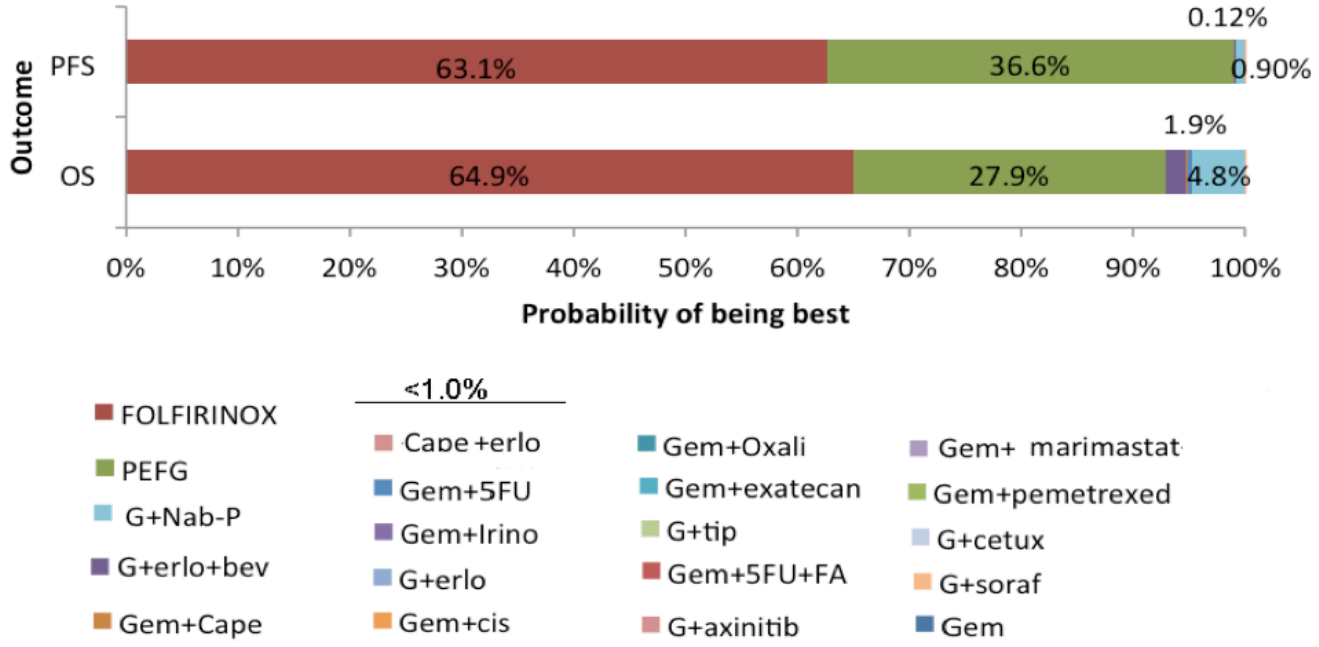
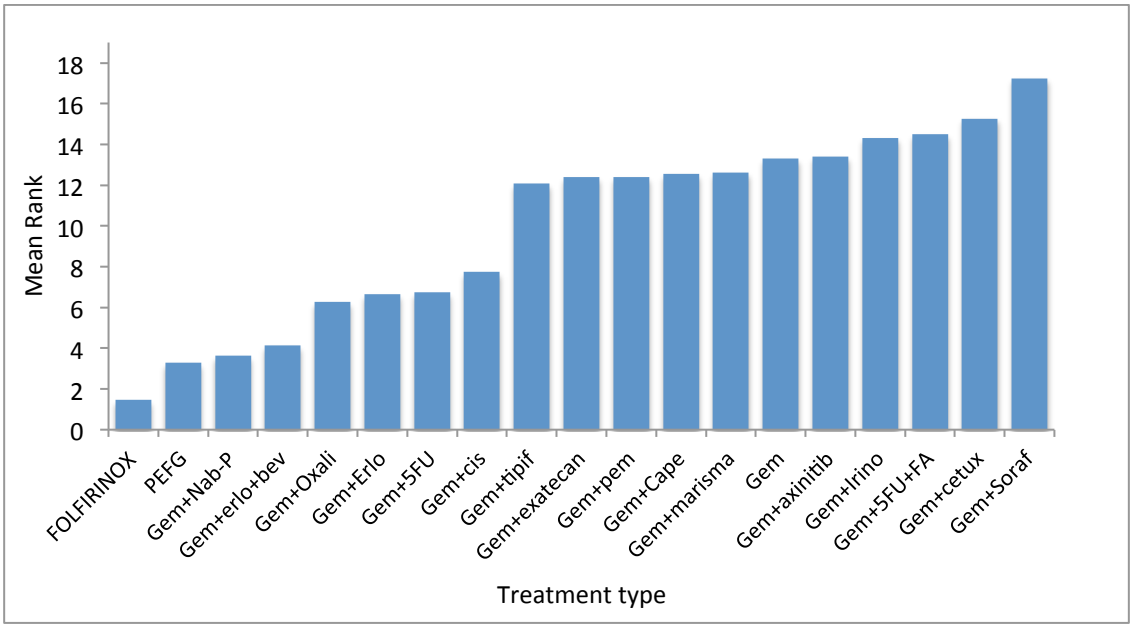
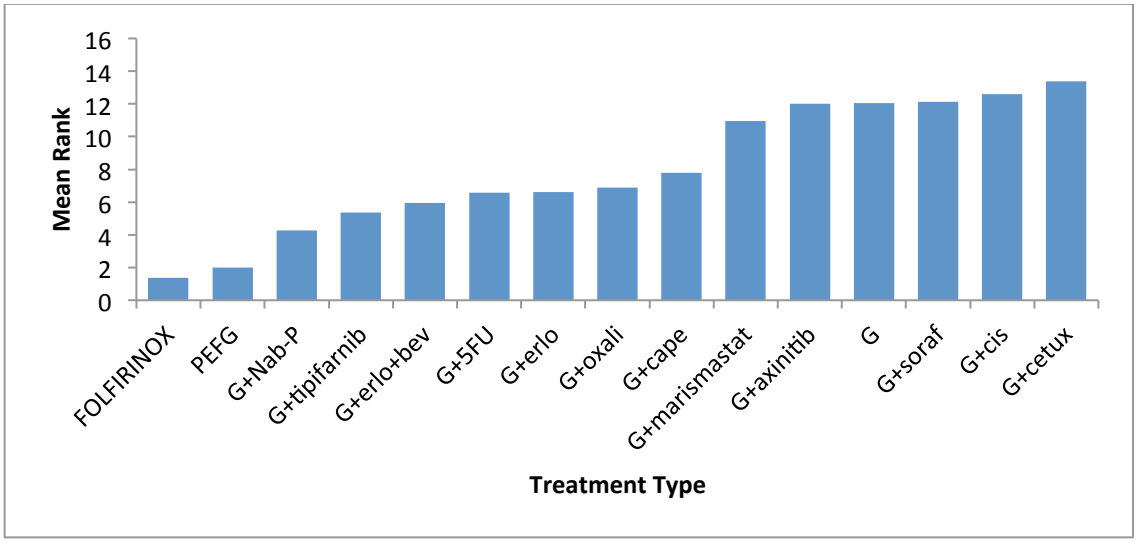


Figure 5: Mean rank for treatments included in Bayesian network meta-analysis for A: Overall survival B: Progression free survival

A



B



** A low mean rank indicates the greatest overall survival relative to other treatments*

The combination of gemcitabine, erlotinib and bevacizumab was ranked fourth for survival outcomes, with a mean rank of 4.14, although a statistically significant benefit was not achieved in the indirect

comparisons with the other treatments. It was found to have a 4.73% probability of being best treatment (Figure 4).

In this multi-treatment comparison, the combination of gemcitabine and sorafenib was associated with statistically significant worse survival outcomes in comparison to five out of nineteen treatments for overall survival (FOLFIRINOX, PEFG, Gem+erlotinib+bev, Gem+erlotinib, Gem+Oxali). It was ranked last for overall survival with a mean rank of 17.23 of 19 treatments and had a 0% probability of being greatest. In terms of progression free survival it had a mean rank of 12.14 out of 15 treatments.

3.4.5. Subgroup analysis for major outcomes

Subgroup analysis adjusting for important covariates such as trial sample size, stage mix, and performance status was performed for the major outcome, overall survival (Table 5).

Table 5: Summary of subgroup characteristics for included trials in the network meta-analysis

Study: Author	Study : Year	Treatment comparison			Proportion of males (%)	Proportion Stage IV (%)	Proportion ECOG 0-1	Proportion KPS 90-100
Bramhall	2002	Gemcitabine	*vs.*	Geme+Marismastat	57.50%	59.80%		86
Berlin	2002	Gemcitabine	*vs.*	Gem+5FU	51.80%	78.50%	85	
VanCustem	2004	Gemcitabine	*vs.*	Gem+Tipifarnib	57.5	76.50%		60
Viret	2004	Gemcitabine	*vs.*	Gem+Cisplatin	NR	81.00%	79.5	
Rocha Lima	2004	Gemcitabine	*vs.*	Gem+Irino	57.20%	82.20%	76.1	
Oreilley	2004	Gemcitabine	*vs.*	Gem+Exatecan	55	78.50%		51.5
Louvet	2005	Gemcitabine	*vs.*	Gem + Oxaliplatin	53%	70.00%	52.7	
Reni	2005	Gemcitabine	*vs.*	Gem+epirubicin+cisplatin+5FU	46.20%	71.00%		72
Riess	2005	Gemcitabine	*vs.*	Gem+5FU+FA	NR	76.50%		54.5
Herrmann	2007	Gemcitabine	*vs.*	Gem+ Capecitabine	54%	79.50%		53
Oettle	2005	Gemcitabine	*vs.*	Gem+Pemetrexed	60.40%	91.10%	86.2	
Abou-Alfa	2006	Gemcitabine	*vs.*	Gem+Exatecan	55.50%	79.00%		56
Heinemann	2006	Gemcitabine	*vs.*	Gem+Cisplatin	65.30%	79.50%		52.5

Poplin	2006	Gemcitabine	*vs.*	Gem + Oxaliplatin	45.60%	88.60%	87.4	
Moore	2007	Gemcitabine	*vs.*	Gem+Erlotinib	52.40%	75.70%	81.2	
Cunningham	2009	Gemcitabine	*vs.*	Gem+ Capecitabine	59%	71.00%	81	
VanCustem	2009	Gem+Erlotinib	*vs.*	Gem+Erlotinib+ Bevacizumab	62.00%	100.00%	85	
Philip	2010	Gemcitabine	*vs.*	Gem + Cetuximab	54%	79.00%	82	
Colucci	2010	Gemcitabine	*vs.*	Gem+Cisplatin	59.50%	83.80%		82.7
Kindler	2011	Gemcitabine	*vs.*	Gem+Axinitib	60%	72.00%	100	
Conroy	2011	Gemcitabine	*vs.*	FOLFIRINOX	30.70%	100.00%	99	
Goncalves	2012	Gemcitabine	*vs.*	Gem+Sorafenib	59.60%	79.80%	92	
Von Hoff	2013	Gemcitabine	*vs.*	Gem+ nab-Paclitaxel	58.00%	100.00%		60

In order to address possible heterogeneity between trial populations with regards to covariates such as trial sample size, year of publication, stage mix, and performance status, various subgroup analyses were performed for the primary outcome, OS.

In the subgroup analysis of trials including at least 100 patients per arm, 19 trials involving 17 different treatments were included (Table 3). Trials that were excluded in this sensitivity analysis are identified in Table 3. FOLFIRINOX was ranked first for OS and PFS followed by gemcitabine +NAB-Paclitaxel and gemcitabine+erlotinib+bev in this subgroup network meta-analysis. FOLFIRINOX was associated with statistically significant hazard ratios for OS over all treatments except for gemcitabine+NAB-Paclitaxel (HR: 0.85 95% Cl 0.47-1.33) and gem+erlotinib+bevacizumab (HR: 0.90, 95%Cl 0.41-1.48).

A sensitivity analysis excluding studies published prior to 2007 resulted in ten included studies where FOLFIRINOX was ranked first followed by gemcitabine+NAB-Paclitaxel, which was ranked second, and gemcitabine+erlotinib+bevacizumab, ranked third (Table 3). Hazard ratios were very similar to the hazard ratios found in other sensitivity analyses and overall results.

In the sensitivity analysis in which only trials where the proportion of patients with metastases was less than 80% were excluded, 8 trials were excluded from the analysis (Table 3). FOLFIRINOX was ranked first for OS and associated with statistically significant hazard ratios for 9 out of 15 possible

combinations, but not gem+NAB-P, gem+erlotinib+bevacizumab, gem+erlotinib, gem+oxaliplatin and gem+capecitabine.

Finally, the sensitivity analysis for poor performance status excluded seven trials which included a proportion greater than 85% of patients with ECOG 0-1 (or KPS equivalent) Conroy (2010) and Reni (2005),Goncalves (2012), Kindler (2011), Conroy (2011), Poplin (2006), Oettle (2005), and Bramhall (2002) (Table 3). In this analysis, Gemcitabine+NAB-Paclitaxel RCT, enrolling 60% patients with KPS 90-100, was ranked first for OS and was associated with statistically significant hazard ratio for survival over gemcitabine alone (HR: 0.72, 95% CI (0.54-0.95)]. Gemcitabine+erlotinib/bev and gemcitabine+bev were also associated with significant OS over gemcitabine alone.

3.4.6. Minor Outcomes

Decided a priori, stage four neutropenia, febrile neutropenia, diarrhea, sensory neuropathy and vomiting were assessed in the multiple treatments comparison. Odds ratios and 95% Cl were obtained for each comparison of each grade 3 or 4 toxicity as per the CTCAE v 3.7, and treatments were ranked in order of highest toxicity rates to lowest based on the odds ratios found in the comparison. FOLFIRINOX was associated with statistically significant overall response rate (ORR) relative 10 of 18 regimens, excluding gemcitabine+ nab paclitaxel, Gemcitabine+erlotinib+bevacizumab (OR 2.61 0.96-7.24), gemcitabine+pemetrexed, gemcitabine and irinotecan or PEFG.

Thirteen treatments were evaluable for grade ¾ febrile neutropenia where statistically significant differences were observed between gemcitabine alone *versus* FOLFIRINOX, gemcitabine+NAB-P, gemcitabine+Pemetrexed and Gemcitabine+Irinotecan. Gemcitabine+Pemetrexed was ranked highest for risk of grade ¾ febrile neutropenia being associated with statistically significant odds ratios over gemcitabine alone, gemcitabine+NAB-Paclitaxel, gemcitabine+ cisplatin, and gemcitabine+oxaliplatin. It was not statistically different than FOLFIRINOX. No other treatments were found to be associated with statistically significant odds ratios relative to each other in this analysis.

Grade 3/4 neutropenia was reported in sixteen trials included in the network meta-analysis. Gemcitabine+capecitabine, gemcitabine+cisplatin, Gemcitabine+5FU/FA, PEFG, FOLFIRINOX, gemcitabine+erlotinib+bevacizumab, gemcitabine+tipifarnib and gemcitabine+NAB-P were associated with statistically significant increased risk for grade 3/4 neutropenia over gemcitabine alone. PEFG was

ranked highest with statistically significant odds ratios relative to gemcitabine+cisplatin, gemcitabine+capecitabine, gemcitabine+5FU+/-FA, gemcitabine+irinotecan, gemcitabine+exatecan, FOLFIRINOX, gemcitabine+NAB-P, gemcitabine+erlotinib+/- bevacizumab and gemcitabine+tipifarnib. It did not statistically differ from gemcitabine + pemetrexed. FOLFIRINOX was associated with statistically significantly greater odds for grade 3/4 neutropenia in comparison to gemcitabine + NAB-Paclitaxel (OR: 1.92, 95%CL 1.10-3.39), gemcitabine+cisplatin, gemcitabine+capecitabine, gemcitabine+tipifarnib and gemcitabine+erlotinib+bevacizumab. FOLFIRINOX was ranked as the second treatment most associated with grade 3/4 neutropenia after PEFG.

For grade 3/4 diarrhea, gemcitabine+oxaliplatin, gemcitabine+cisplatin, gemcitabine+pemetrexed, FOLFIRINOX, gemcitabine+NAB-Paclitaxel and gemcitabine+erlotinib were associated with significantly greater odds for diarrhea compared to gemcitabine alone. FOLFIRINOX and Gemcitabine+NAB-Paclitaxel had comparable outcomes in terms of grade ¾ diarrhea and were ranked first and second for increased risk of grade ¾ diarrhea, respectively. They were both significantly associated with increased risk for grade ¾ diarrhea relative to the combinations of gemcitabine with cisplatin, capecitabine, erlotinib with or without bevacizumab, sorafenib, axinitib, and 5FU/FA. In this analysis, gemcitabine+erlotinib+bevacizumab had the lowest risk for grade ¾ diarrhea.

In the analysis of grade 3/4 fatigue, gemcitabine+NAB-Paclitaxel and gemcitabine+pemetrexed were associated with statistically significant odds ratios over gemcitabine alone. Gemcitabine+NAB-Paclitaxel was associated with statistically significant odds ratios for grade 3/4 fatigue over eight other treatments: Gemcitabine alone; Gemcitabine +Tipifarnib, Gemcitabine+Exatecan; Gemcitabine+Oxaliplatin; Gemcitabine+erlotinib; Gemcitabine+Capecitabine; Gemcitabine+cetuximab; Gemcitabine+Erlotinib/Bevacizumab. Gemcitabine+NAB-Paclitaxel was ranked highest for risk of grade 3/4 fatigue with a mean rank of 14.68 out of the 16 evaluable treatments. It was not statistically different than gemcitabine+pemetrexed, PEFG, gemcitabine+cisplatin or FOLFIRINOX, although it trended towards increased risk in comparison to FOLFIRINOX (OR: 1.90, 95% CL 0.94-3.88) (Figure 6).

Gemcitabine+cisplatin, gemcitabine+oxaliplatin, gemcitabine+cetuximab and cisplatin+exatecan were associated with a statistically significant increase of risk for grade 3/4 vomiting over gemcitabine alone. Gemcitabine+cisplatin and gemcitabine+oxaliplatin was had statistically significant odds ratios relative

to PEFG, gemcitabine+marismastat, gemcitabine+5FU and gemcitabine+tipifarnib. Gemcitabine+exatecan and FOLFIRINOX were both associated with significant odds ratios over gemcitabine+tipifarnib. Grade 3/4 vomiting in patients treated with gemcitabine+NAB-Paclitaxel was not evaluable in this analysis as data was not available.

FOLFIRINOX was ranked worse for grade 3/4 sensory neuropathy out of six treatments with available data (gemcitabine+Oxaliplatin, gemcitabine+cisplatin, gemcitabine+tipifarnib and gemcitabine+NAB-P). All included treatments in the analysis had statistically significant increased risk for grade ¾ sensory neuropathy compared to gemcitabine alone. However, none of them were found to be associated with statistically significant odds ratios over other included treatments.

Overall, there were no statistically significant differences in odds ratios for febrile neutropenia, fatigue, diarrhea or sensory neuropathy between FOLFIRINOX versus gemcitabine plus NAB-Paclitaxel with the exception of grade 3/4 neutropenia (Figure 6).

3.5. Discussion

Advanced pancreatic cancer remains a deadly disease and progress in its treatment has been slow. Since gemcitabine was established as the standard therapy, only modest improvements in outcomes have been achieved. Initial efforts to combine gemcitabine with other therapies in the form of doublets lead to a stream of statistically negative trials that were redeemed only through meta-analysis suggesting some benefit for combination with platinums or capecitabine. In contrast, recent large multi-center trials offer promising results with regimens including FOLFIRINOX[28] and gemcitabine+ nab-paclitaxel[26]. In selecting some of these regimens (FOLFIRINOX, PEFG), investigators have abandoned the traditional stepwise approach of adding a single new agent to assess the specific contribution of that agent to outcome. This approach, while hazy from a regulatory and purely scientific perspective, has met with considerable success. However, survival benefits with these more aggressive treatment must be weighed against the greater risk of toxicity from these treatments.

Most systematic reviews focus on direct comparisons of the treatments and it is often difficult to determine the most effective treatment[72-79]. Most recently, Hu et al (2011) conducted a systematic

review and meta-analysis of 35 phase II and III trials for advanced pancreatic cancer[11]. They found that gemcitabine based combination therapies were significantly better for overall survival and progression free survival with gemcitabine plus capecitabine being associated with enhanced survival benefits. A benefit for gemcitabine based combinations were also found in a meta-analysis conducted by Sultana *et al* (2008) who had also analyzed the safety profile of these combination therapies and concluded that although they demonstrated a greater survival benefit, they were also associated with greater toxicities than gemcitabine alone[78]. These meta-analyses, however, reflect only the results of direct comparisons and information about safety and treatment rankings are limited.

In the absence of head to head trials comparing these new combinations, indirect comparisons allow for determination of optimal therapy. We performed a network meta-analysis that evaluates the efficacy and tolerability of treatments available for advanced pancreatic cancer up to 2013, including four new treatments that have not yet been evaluated in a previously published meta-analysis [20, 23,24,26,28].

Study quality was assessed to gain awareness of possible biases that may exist within each included clinical trial. Using the Sign 50 scale, most studies met quality standards, however the majority of trials that were labeled as adequate (+) due to concerns about the trial's internal validity in particular with regards to blinding. It is debatable whether the lack of double blinding can bias the results or not. Schultz et al. reported that the lack of double-blinding was associated with larger treatment effects while Moher *et al* did not find a significant relationship[80-83]. The rationale between lack of blinding for the RCTs comparing treatments for advanced pancreatic cancer are that hard outcomes are being assessed such as overall mortality, progression free survival and response rate. These outcomes can be measured objectively, and the importance of double blinding becomes much less relevant. Another assessment of methodological quality includes the quality of reporting where the extent of information on the design, conduct and analysis of the trial could have an impact on the overall quality assessment. It was found in the quality assessment of this study that almost half the trials assessed did not report important details around the methodology and conduct of the trial. This has also been supported in the literature where trials frequently omit important methodological details[80-84].

This study allowed for the indirect comparisons between FOLFIRINOX and nab-paclitaxel as well as seventeen other eligible treatments that have been tested over the past decade. By using Bayesian statistics to accomplish a mixed-treatment analysis, high-quality information on the effectiveness and safety of each treatment was achieved. One of the advantages and thus rationale behind selecting a Bayesian network meta-analysis over a frequentist meta-analysis was that it the Bayesian methods allowed for the calculation of the probability of a treatment being best, and the ranking of the various treatments, which is important for medical decision-making and can ultimately lead to the determination of the optimal therapy. Because there were so many treatments included in the network, and it was unclear of which treatment offered the best survival advantages and by how much, the Bayesian network meta-analysis permitted a straightforward way of making decisions[70]. Important findings from this study include the statistically and clinically significant survival benefit of FOLFIRINOX over the majority of treatments (>75%) with a median survival gain of 4 months. Of interest, safety outcomes for FOLFIRINOX were comparable to the other combination treatments where no statistically significant difference in odds ratios were observed for grade 3 or 4 adverse events including vomiting, diarrhea, sensory neuropathy or febrile neuropathy in comparison to the combination of gemcitabine and nab-paclitaxel or the PEFG regimen. Of note, FOLFIRINOX was associated with a significantly greater risk for grade 3 or 4 neutropenia, which is of clinical relevance especially in patients with endobiliary stents. In contrast, the risk of grade 3 or 4 fatigue trended lower with FOLFIRINOX than with gemcitabine plus nab-paclitaxel.

PEFG was found to have significant survival and progression free survival advantages over gemcitabine alone as well as five other treatments in the multiple comparisons, but credible intervals were wider as it was limited by a small trial sample size (N=104). Further studies will be needed to confirm these results.

In comparison to gemcitabine-based doublets, our ranking found that FOLFIRINOX and PEFG offer an even greater survival advantage. FOLFIRINOX and PEFG were ranked first and second respectively for all patient outcomes including overall survival, progression free survival and overall response rate. Although PEFG was found to be associated with statistically significant survival outcomes and appeared to be a good regimen, it was not found to be superior to FOLFIRINOX. As the PEFG regimen shares similarities with FOLFIRINOX, being a four-drug combination therapy associated with greater risk of

toxicities, there is less value to pursue this therapy, as it was outperformed by FOLFIRINOX in terms of rankings and magnitude of effect estimates for survival outcomes. FOLFIRINOX was found to have a statistically significant benefit in survival outcomes over the majority of gemcitabine-based combination therapies except for PEFG, gemcitabine+erlotinib+bevacizumab and gemcitabine+nab-paclitaxel. The combination of gemcitabine and nab-paclitaxel was ranked third for survival outcomes but first for gemcitabine-based doublets. However, it was not found to have a statistically significant difference in overall survival and progression free survival over gemcitabine+capecitabine, gemcitabine+platins or gemcitabine+5FU. When analyzed in a sensitivity analysis for performance status though, where FOLFIRINOX and PEFG were excluded from this analysis, gemcitabine and nab-pacletaxel offered the greatest survival benefit in patients who may have worse performance status. The FOLFIRINOX trial involved 99% of patients with ECOG PS 0-1 and thus enrolled a population of patients with better overall performance status. Gemcitabine+nab-paclitaxel could potentially be considered as an option for patients with worse performance status, although it was found to be associated with significant grade 3 and 4 fatigue.

This network meta-analysis provides an overall idea of the benefits and risks that each treatment may offer on a relative scale, using hazard ratios as the preferred time-to-event measures. Our network meta-analysis relays important information about the general efficacy and tolerability of treatments in a timely manner with no associated costs. Results from the network meta-analysis can guide physicians in the recommendations of different treatments while awaiting results from ongoing clinical trials. The cost of conducting multi-center trials in order to compare all of the treatments found to have a statistically significant survival benefit would be considerable, and results may not be conclusive. Furthermore, there would arguably be no clear overall benefit for patients with pancreatic cancer.

3.5.1. Limitations

Limitations of this study include the fact that this analysis was performed on the assumption of consistency where the validity of indirect comparisons was determined by the extent of clinical and methodological trial similarity. Differences in study populations, interventions, trial design, and outcomes definitions were therefore potential sources of biases or errors. Also, not all primary outcomes or adverse event outcomes of interest were reported consistently. Thus the number of trials included in each network meta-analysis varied between outcomes, where there were nineteen trials

included in the analysis for overall survival, 15 for progression free survival and 18 for overall response rate. Adverse events were not all reported across trials, particularly for febrile neutropenia and sensory neuropathy, as these events are specific to certain drugs. This missing data caused credible intervals to be much larger, with uncertainty around the estimates. Furthermore, in cases where no events had occurred for the outcome of interest, a continuity correction was added in order to allow the analysis[85]. Due to different methods that are used for reporting quality of life, it was not assessed in this network meta-analysis.

The geometry of the network presented, with only single comparisons available, may also lead to possible limitations. While closed networks may provide more robust results, allow one to evaluate the underlying assumptions and consistency and allow for the comparison of the direct estimates with the indirect, the open network in the present study is limited by the amount of available studies per comparison.

Finally, some baseline differences in trial populations may have affected the outcomes. For example, FOLFIRINOX included better prognosis patients (99% ECOG performance status of 0-1) and had a larger majority of males in the study, which may have altered effect estimates. Hazard ratios should be used as guides for physicians and not as definitive values.

3.5.2. Conclusion

Overall, FOLFIRINOX was found to demonstrate a statistically significant survival advantage over gemcitabine alone as well as the majority of other gemcitabine-based combination therapies. However, FOLFIRINOX was not associated with statistically significant survival outcomes over gemcitabine +nab-paclitaxel thus the clinical relevance of this difference is inconclusive. Whether these two treatments should be tested in a large multi-center randomized clinical trial, or whether the choice of treatment is left to the physician's discretion is up for debate. The use of network meta-analysis in these settings can be very informative and cost-beneficial, and the periodical updates of the analysis will be important in guiding physicians and researchers to the development of more beneficial treatments for advanced pancreatic cancer. It may also help direct the design of future clinical trials.

4. DEVELOPMENT AND DESIGN OF A CLINICAL DECISION AID FOR PATIENTS WITH METASTATIC PANCREATIC CANCER CONSIDERING CHEMOTHERAPY

4.1. Rationale

As patients have become more involved in decisions around their healthcare, the need for the dissemination of high quality and relevant information has also become important. Decision Aids are tools that communicate information in a way that engages patients in treatment choices that is consistent with the evidence and their personal preferences and values[36]. They are often employed in settings that involve decisions between surgical interventions, screening programs or various other therapeutic decisions where more than one suitable treatment option is available for the patient.

The majority of decision aids that have been designed for patients in the oncology setting include those for patients with early-stage diagnoses considering different adjuvant therapies or surgeries. There are less decision aids available for patients with advanced cancers, although some have been designed for patients with advanced colorectal, breast and prostate cancer[86-90]. In advanced cases, decisions can be even more complex as patients are not only deciding between the best therapy option for their condition but also whether they would rather pursue best supportive care alone and avoid systemic treatment altogether. To date, there has not been any decision aids published for advanced pancreatic cancer. Due to the late onset of symptoms in patients presenting with pancreatic cancer, this decision is unfortunately faced in over half the presenting population.

When first diagnosed with advanced pancreatic cancer, patients are often referred to the medical oncologist who will assess the patient and advise them on the best treatment choice. During this consultation, patients will be provided with a significant amount of information related to their diagnosis, prognosis and treatment choices. The amount of information can be overwhelming and present as a real challenge for the patients to retain the knowledge and process it in a way that allows them to make a treatment choice that best meets their needs in the course of a one-hour visit. This decision aid was designed with the primary objective of improving a patient's knowledge about the different treatment options available and the benefits and risks that each option presents while decreasing decisional conflict. This was achieved by allowing patients to weigh each of the benefits

that the different treatment options offer against their associated risks or side effects. This is especially important as more aggressive and chemotherapies for pancreatic cancer have been introduced including FOLFIRINOX, a combination of four drugs.

With the added benefits to survival that FOLFIRINOX offers, but increased risk of side effects, a patient will have time to take this tool home to use and go through the information prior to their consultation with their medical oncologist. They can ultimately take more time to process the information and decide on whether they are leaning more towards FOLFIRINOX or a less aggressive option such as gemcitabine, the standard treatment. With information about the different treatment options available, as well as the option for no treatment, patients may feel more informed about their diagnosis, treatment options and preferences and thus, more confident in the decision that they are making. The use of a decision aid prior to consultation with their medical oncologist can also help patients feel more prepared to ask questions and share their values with their doctor in order to participate in the decision making process.

4.2. Objectives

The primary objective of this chapter was first to design and develop an Internet-based patient decision aid to present the different treatment options available to the patients including the option of no treatment; to inform patients of the benefits and risks that each treatment option presents for their disease; and to guide them through the decision making process by asking questions about their individual preferences and values.

4.3. Methods

An Internet-based patient decision aid was developed for patients with advanced pancreatic cancer between August 2012-January 2013 at the Ottawa Hospital Cancer Center and British Columbia Cancer Agency in Canada. The Decision aid was modeled following IPDAS criteria for decision aids[92] checklist within the scope of The Ottawa Decision Support Framework[39, 91]. A detailed summary of the Ottawa

Decision Support Framework and the glossary of decisional terms can be found in Appendices 5 and 6. The complete IPDAS criteria checklist for developing decision aids is included in Appendix 7.

4.3.1. The Ottawa Decision Support Framework

The decision aid was developed following components of the Ottawa Decision Support Framework, a theoretical framework that uses concepts and theories from psychology, social support, amongst other disciplines to provide the best model to physicians, researchers and patients[39, 92,93]. The three components of the framework include decisional needs, decisional quality and decisional support. For the development of this decision aid, decisional needs were clarified by performing a large systematic review and network meta-analysis of treatment options available for this population of patients and summarizing results of a clinician survey to determine the need, the content and format of the decision aid. Needs were then assessed in the pilot study of the decision aid, where patient knowledge and expectations were measured prior to the use of the decision aid. The decisional conflict scale was also used to determine the utility of such a tool in this population of patients. Results from the pilot study will be explained in detail in the following chapter.

Based on the ODSF, decisional quality of this decision aid was informed, where the impact emphasized values-based health outcomes[91]. Using the decision aid, decisional support was provided through the clarification of the decisions that the patients will be facing, the presentation of facts and probabilities related to each treatment option, the clarification of the patients values and the close monitoring and facilitation of the decision making process[91].

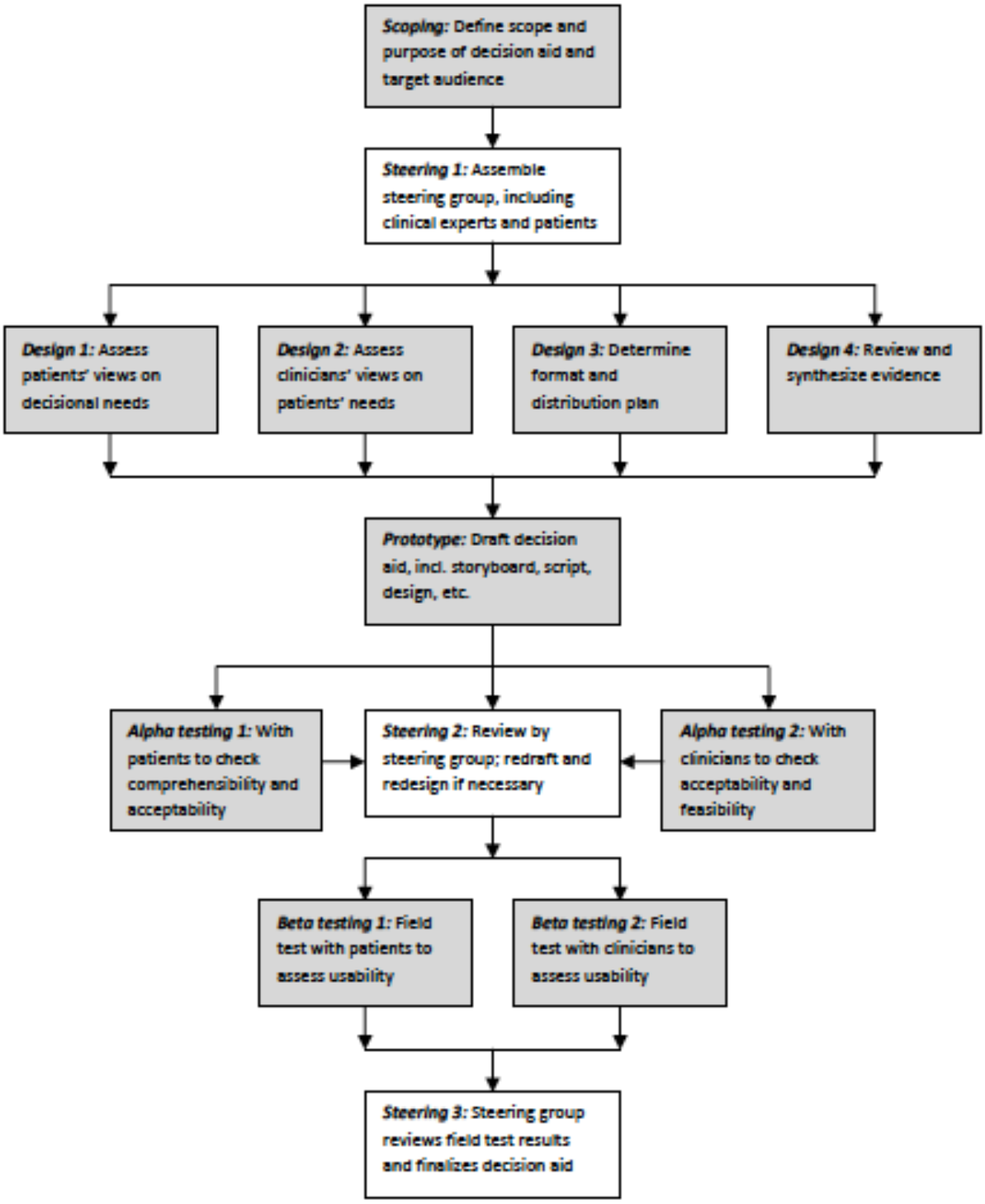
4.3.2. The IPDAS criteria for developing a decision aid

The International Patient Decision Aid Standards (IPDAS) Collaboration includes a group of researchers, practitioners and stakeholders form around the world that was established in 2003 and lead by Dr. Elwyn of the United Kingdom and Dawn Stacey of Ottawa, Canada[92]. The purpose of IPDAS is to enhance the quality and effectiveness of patient decision aids by providing a framework and standard set of criteria in order to improve the content, development implementation and evaluation of

decision aids. Because there are over 500 patient decision aids that have been developed, and more are being developed all the time, the need for a shared evidence-informed framework is important in order for patients to have access to reliable health information presented in a standard way that has been tested and shown to work. The IPDAS framework applies to all participants that are involved in decision-making including the physicians, patients and patients' family. The IPDAS framework consists of three key elements including decisional needs, decision quality and decision support.

Following the IPDAS framework (Figure 6), the design of the decision aid began with defining the scope and purpose of the decision aid and identifying the target audience, which in this case, was advanced pancreatic cancer patients. A group was then assembled to include clinical experts and researchers to provide information and feedback on the content and delivery of the decision aid. The steering committee identified for the purpose of this decision aid included panel of two clinician experts in medical oncology specializing in gastrointestinal cancers; a psychosocial oncologist, from the Psychosocial Oncology Program, and a professor with extensive experience in decision aid design and implementation, from the faculty of epidemiology and community medicine at the University of Ottawa. The committee was responsible for revising and approving the content and development of the decision aid. Following the IPDAS framework in Figure 2, patient and physician's decisional needs and the format and distribution plan were determined. The review and synthesis of the evidence was then gathered through a systematic review and network meta-analysis, summarized in the previous chapter of this thesis. Based on the decisional needs, the prototype was created where a draft decision aid was presented to the review panel in August 2012. It underwent several iterations before being finalized. The first prototype was then prepared for its evaluation of acceptability and feasibility within the patient population as well as with the clinicians. This phase of the framework is presented in the fifth chapter of this thesis.

Figure 5: The IPDAS framework for decision aid development



4.3.3. Information content

Information was obtained from a systematic review and network meta-analysis of all chemotherapy regimens for advanced pancreatic cancer that was tested in randomized clinical trials where gemcitabine was used as the reference comparator (Chapter 3 in this thesis). Effect estimates for survival outcomes were used to compare the different treatment options and to determine the optimal therapy that would be used in the decision aid. FOLFIRINOX was found to be the most effective treatment with a statistically significant survival benefit in over 75% of the available treatments, although it was associated with more toxicity. FOLFIRINOX was therefore included in the decision aid as one of the available treatments. Gemcitabine, the standard therapy is the less aggressive option, as it is a single agent therapy, and was included as a second arm in the decision aid because it has been used as the standard therapy for over twenty years and is a very well-researched and tolerated therapy for patients who may have worse overall performance status. Finally, best supportive care was also included as an option for patients who choose not to pursue any treatment. Best supportive care involves the management of symptoms, improvement of quality of life and of the patient's overall physical and mental well-being. Data extracted from systematic reviews and meta-analyses were interpreted and translated into understandable language to be included in the decision aid. The average readability of the decision aid was grade 8.15 (+/- 0.5). However, the decision aid is considered comprehensible to patients below the grade 8 reading level as well, as the illustrations and graphics that accompany the writing may clarify any patient misunderstanding or incomprehension.

The overall content of the decision aid included information on pancreatic cancer, information on the treatment choices, the first step of the decision aid where patients decide between chemotherapy or best supportive care alone and the second step, where patients decide between gemcitabine and FOLFIRINOX. Information was presented in a balanced manner where both the positive and negative features of each option were clearly stated as per requirements of the IPDAS criteria[94]. Based on the IPDAS definition, the extent to which a decision aid is balanced, is the extent to which it presents the available options and the positive and negative information about each of the options in a complete and neutral manner without influencing individuals towards favouring or rejecting any particular option[94]. As a balanced decision aid results from complete information, efforts were made to conduct a comprehensive and inclusive collection of the evidence and present all associated information in an

objective manner. The objectivity of the decision aid also depends on the format and display of information where efforts were made to present the information using equal detail in terms of font size, order of reporting, and display of statistics. With regards to the presentation of probabilities, referring to the IPDAS chapter on presentation of probabilities, suitable formats included the use of visual aids such as bar charts, human figure representations, 100-face diagrams and flow diagrams[94]. By using the suggested visual aids, several biases could be avoided such as neglecting the denominator, framing effects and undue influence of anecdotes[94].

4.3.4. Selection of the decision aid format:

The Ottawa Decision template was used as a template to create the decision aid, which was then transformed into an online interactive web design in order to allow patients to select links and sub-links as well as to control the amount of information that they wish to access. Following specific IPDAS criteria for Internet-based decision aids, patients were provided with a way to search for key words; printable forms of all pages were available; and navigation through the different pages and links was facilitated by making it easy for patients to return to the decision aid home page after visiting other pages and providing an intuitive step-by-step way to move through the different pages (e.g. following pages from top to bottom/left to right, using numbered lists, *etc*.) Patient privacy was also protected, where patients were only asked for their randomly assigned study number when providing their responses to the different questions. The website was created using Google Sites and Google Drive. The website was created and programmed entirely by the primary author (GG). The website URL to access the decision aid is: https://sites.google.com/site/decisionaid4pancreaticcancer/. The complete printed version of the decision aid can be found in Appendix 8.

4.3.5. Components of the decision

The primary objective of this decision aid was to guide patients through two different steps of the decision making process: The first being the decision between having chemotherapy or no chemotherapy (best supportive care alone), and the second, for patients leaning towards chemotherapy, between FOLFIRINOX or gemcitabine (Figure 7). The patient decision was divided into six components, based on the four major outcomes of interest reported in the literature: Overall Survival; Cancer Control (Progression Free Survival); Side effects; Quality of life, and two additional outcomes that may contribute to a patient's overall well-being: Symptom Management and Convenience.

Overall Survival (OS) is the time from enrolment until death from any cause, measured in the intent-to-treat population. Overall Survival was measured by the event of death of a patient. Progression-Free Survival (or cancer control) is the time from start of treatment to disease progression or death due to any cause. Progressive disease is an event that can be objectively evaluated from eight-week radiological assessments (CT scans). These evaluations are compared to the baseline scan at each assessment. Patient safety includes information on all adverse events or side effects caused by the treatment that a patient might experience. Finally, Quality of Life is Patient reported outcome, which is often measured by scales such as EORTC QLQ-C30 scale v3 and FACT.

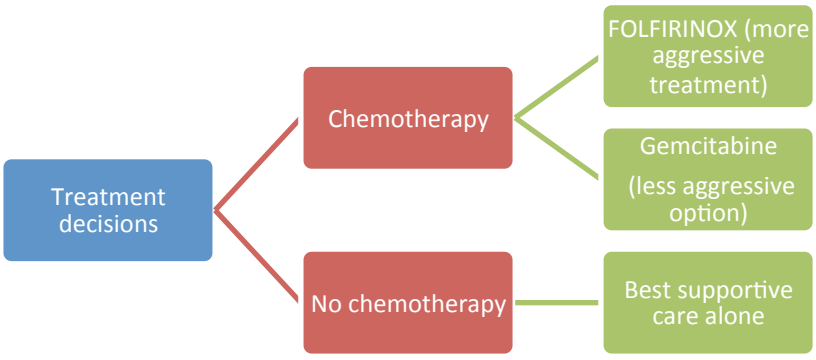
4.4. Results

4.4.1. Decision aid content

The decision aid was divided into four principle panels: the description of the health condition; the treatment options being evaluated the probabilities of outcomes and positive and negative features of the different treatment choices, updated information about the disease and treatment options, and then the decision aid itself, which was further subdivided into the two decisions a patient with pancreatic cancer will be facing. Components of the decision aid included information about the decision to be made; the benefits and risks of each treatment option separated by outcome type (survival, quality of life, *etc.*); communication and clarification of the patient values in terms of what is

important to them for each component of the decision; and finally, the summary and identification of the patient's values and preferences and next steps.

Figure 6: Decision tree for the development of a decision aid for patients with advanced pancreatic cancer considering chemotherapy



A simple Internet-based design was used to allow for patients to comfortably navigate through the website and access all the information they desire to view (Figure 8). The home page presents a title of the webpage and brief description of the objective and purpose of this webpage below the title as well as a panel of four different links. Each link is provided with a picture and a title presented in the form of a question. For instance, reading from left to right, the different titles are: "What is pancreatic cancer"; "What are my treatment options"; "Is chemotherapy right for me?"; "Which chemotherapy type is right for me?" On the right side bar, there is a disclaimer indicating patient eligibility for the use of the decision aid in order to clearly identify the target population for this tool prior to its use. Below the disclaimer, several links are included for patients to access the decisional conflict questionnaire, the patient knowledge test, and the acceptability and feasibility questionnaires. The patients' responses to these questionnaires will be summarized and reported as part of the final results of the needs assessment and pilot study of this decision aid presented in the next chapter. Essentially, a user of this decision aid would begin by reading the information presented on pancreatic cancer found in the first panel, a detailed description of their treatment options and then would be guided through the first step of the decision aid, which includes the choice between best supportive care alone and chemotherapy (any). If results from the decision aid indicated that the patient may want to think about

pursuing chemotherapy, they were then led to the second part of the decision aid, where a decision between two different types of treatments, FOLFIRINOX and gemcitabine would be made. If a patient were to choose not to pursue any treatment, they would then be guided towards more information about best supportive care alone. Once the patients' answers are submitted, feedback can be provided to the patient in a visual manner, where they can then choose to print the results and share with their oncologist during their consultation.

Figure 7: Screen capture of the decision aid website homepage, as viewed by patients

**Underlined writing in turquoise represents a link to another web page, which provides information about the question of interest or provides the decision aid tool.*

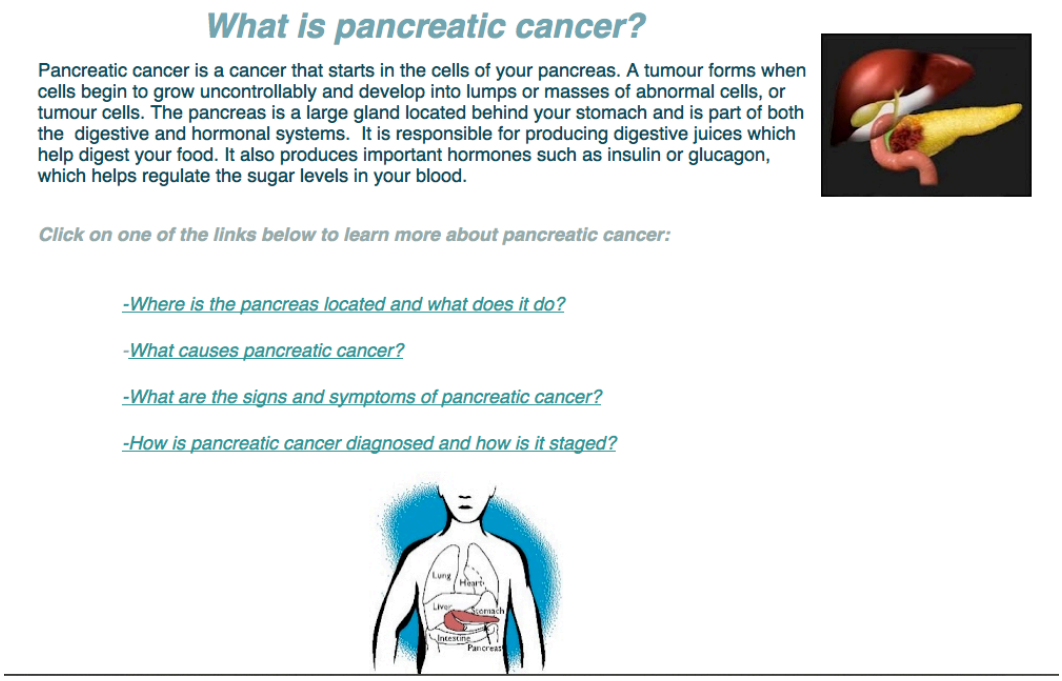
4.4.2. Description of the health condition

Following the sub-criteria of the IPDAS, information about options, probabilities of outcomes, methods for clarifying and expressing patients' values and structured guidance in deliberation and communication were included as part of the decision aid content[92].

First, in order to increase patient knowledge and improve realistic expectations, information was provided in sufficient detail to allow patients to access and read current research about their diagnosis and the treatments available to them prior to completing the decision aid. The first link of the website

brings patients to a new page that describes the health condition of interest: pancreatic cancer. The page includes the general definition of pancreatic cancer followed by a list of links that will bring patients to more specific information about the disease including questions about the location of the pancreatic tumour, signs and symptoms of pancreatic cancer, staging of pancreatic cancer and risk factors (Figure 9).

Figure 8: Screen capture of decision aid information page on pancreatic cancer after a patient selects the link "*What is pancreatic cancer?*"



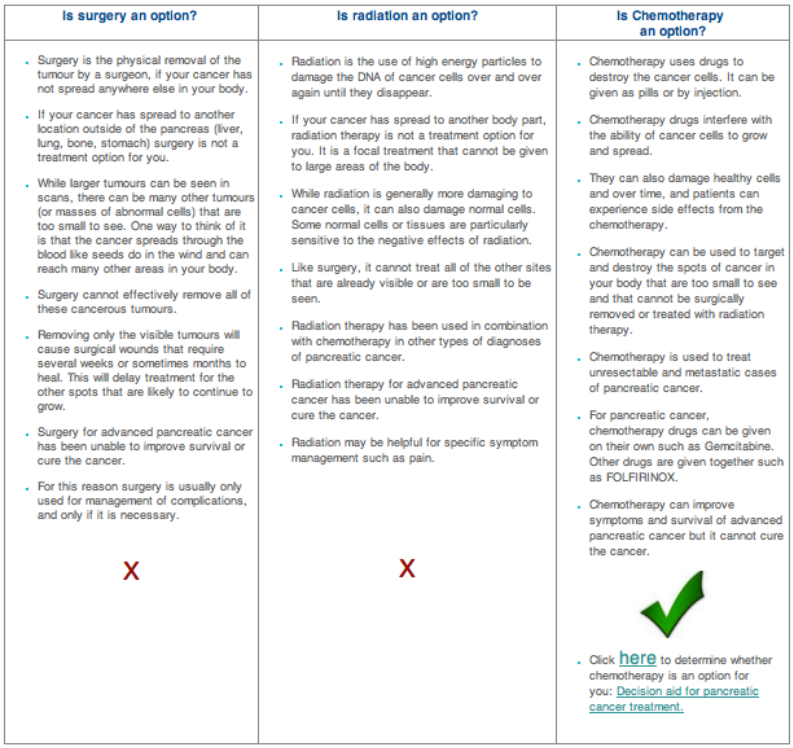
**Underlined writing in turquoise represents a link to another web page, which provides information in more depth based on each question.*

4.4.3. Listing the options

Patients may not only wish to know what their treatment options are, but also what treatment options do not apply to them for their specific diagnosis. For instance, patients with metastatic pancreatic cancer are not eligible for treatment with surgery or radiation due to the extent of their disease and localized nature of these particular treatments. In the second panel of the website, "What are my

treatment options?" reasons for why certain treatments are not applicable to their situation and why chemotherapy is the best treatment option are outlined in a comparison table (Figure 10). The definition of each treatment choice is included at the top of the table, and then detail about why a patient may or may not be eligible for this treatment is outlined below. At the bottom of the table, a red "X" indicates that this option is not available to the patient and a green checkmark indicates that it is. Chemotherapy is the only treatment choice for this particular diagnosis, therefore a link to the decision aid where patients can then decide between chemotherapy or best supportive care alone is provided. Furthermore, the option of not pursuing any form of chemotherapy, or best supportive care alone, is included in a separate link and described to patients in a way that patients are aware that this option is also available to them.

Figure 9: Screen capture of the decision aid information page on treatment options



Is surgery an option?	Is radiation an option?	Is Chemotherapy an option?
• Surgery is the physical removal of the tumour by a surgeon, if your cancer has not spread anywhere else in your body. • If your cancer has spread to another location outside of the pancreas (liver, lung, bone, stomach) surgery is not a treatment option for you. • While larger tumours can be seen in scans, there can be many other tumours (or masses of abnormal cells) that are too small to see. One way to think of it is that the cancer spreads through the blood like seeds do in the wind and can reach many other areas in your body. • Surgery cannot effectively remove all of these cancerous tumours. • Removing only the visible tumours will cause surgical wounds that require several weeks or sometimes months to heal. This will delay treatment for the other spots that are likely to continue to grow. • Surgery for advanced pancreatic cancer has been unable to improve survival or cure the cancer. • For this reason surgery is usually only used for management of complications, and only if it is necessary.	• Radiation is the use of high energy particles to damage the DNA of cancer cells over and over again until they disappear. • If your cancer has spread to another body part, radiation therapy is not a treatment option for you. It is a focal treatment that cannot be given to large areas of the body. • While radiation is generally more damaging to cancer cells, it can also damage normal cells. Some normal cells or tissues are particularly sensitive to the negative effects of radiation. • Like surgery, it cannot treat all of the other sites that are already visible or are too small to be seen. • Radiation therapy has been used in combination with chemotherapy in other types of diagnoses of pancreatic cancer. • Radiation therapy for advanced pancreatic cancer has been unable to improve survival or cure the cancer. • Radiation may be helpful for specific symptom management such as pain.	• Chemotherapy uses drugs to destroy the cancer cells. It can be given as pills or by injection. • Chemotherapy drugs interfere with the ability of cancer cells to grow and spread. • They can also damage healthy cells and over time, and patients can experience side effects from the chemotherapy. • Chemotherapy can be used to target and destroy the spots of cancer in your body that are too small to see and that cannot be surgically removed or treated with radiation therapy. • Chemotherapy is used to treat unresectable and metastatic cases of pancreatic cancer. • For pancreatic cancer, chemotherapy drugs can be given on their own such as Gemcitabine. Other drugs are given together such as FOLFIRINOX. • Chemotherapy can improve symptoms and survival of advanced pancreatic cancer but it cannot cure the cancer.
X	X	✓
		• Click here to determine whether chemotherapy is an option for you: Decision aid for pancreatic cancer treatment.

4.4.4. Describing the benefits, risks and probabilities:

The two different steps of the decision aid are included at the bottom of the home page, starting with the decision between chemotherapy or best supportive care alone on the left, and between gemcitabine and FOLFIRINOX on the right.

While answering questions of the decision aid, patients are presented with a list of additional links on the right side bar that provides information on the associated benefits, risks and probabilities of each treatment option for each component of the decision making process. Six outcomes were selected as the founding components of a patient's decision, as utilized in numerous randomized clinical trials and systematic reviews of treatments for advanced pancreatic cancer. The included outcomes were: overall survival; cancer control; avoiding side effects; symptom management; quality of life; and convenience. A summary of all benefits and risks was also provided for patients to view an overall comparison of the benefits and risks for each treatment (Figure 11).

Figure 10: Overview of benefits and risks associated with each treatment option available for patients with advanced pancreatic cancer

BENEFITS/RISKS	(Best supportive care alone)	Gemcitabine	FOLFIRINOX
ADVANTAGES/ BENEFITS ☺= Advantage 😐= Neutral	-Avoiding side effects caused by chemotherapy such as ☺: - Hair loss -Nausea and vomiting -Diarrhea -Risk of infection -Sensitive palms of hands and soles of feet, tingling sensation in fingers, sensitivity to cold or hot temperatures -More convenient😐: -less time spent at hospital. -less visits -less time needed to take off work -less associated costs.	-Survival time longer than with best supportive care alone ☺ -Cancer more controlled than if left untreated ☺ Cancer may: 1) Shrink (9%) ☺ 2) Stay stable (42%) 😐 -May treat cancer-related symptoms ☺ -Quality of life gets worse at a slower rate than with best supportive care alone ☺ -Avoids some side effects caused by FOLFIRINOX (numbness and tingling of hands; sensory neuropathy) ☺	-Survival time longer than with gemcitabine or any other treatment available ☺ -Cancer more controlled if treated with FOLFIRINOX ☺ Cancer may: 1) Shrink (32%) ☺ 2) Stay stable (39%) 😐 -May treat cancer-related symptoms to a greater extent than gemcitabine alone ☺ -Quality of Life gets worse at a slower ra than if treated with gemcitabine alone ☺
DISADVANTAGES/ RISKS ☹=Disadvantage 😐= Neutral	-Survival time is shorter with best supportive care alone ☹ -Cancer may continue to grow faster than if treated with chemotherapy ☹ -Symptoms from cancer can become worse such as pain, fatigue and loss of appetite ☹ -Quality of life will not improve and may worsen over a shorter period of time 😐	-Survival time is shorter with gemcitabine than with FOLFIRINOX ☹ -Risk of side effects from gemcitabine including fatigue, nausea/vomiting, diarrhea… ☹ -Cannot cure the cancer ☹	-More toxicities in patients treated with FOLFIRINOX ☹ -More risk of developing side effects suc as diarrhea, nausea/vomiting, risk of infection (neutropenia/febrile neutropenia), fatigue… ☹ -Cannot cure the cancer ☹ -May be less convenient (more time spe at hospital, must wear infusion pump, associated costs) 😐
The more aggressive a treatment, the greater the risk of side effects, but the longer the survival and cancer control time:			
		Increased risk of side effects	
		Increased survival time	

When comparing the probabilities, visual diagrams were combined with other methods of viewing probabilities such as words, numbers and diagrams to communicate the data across all learning types. Following the ODSF template, visual statistics were displayed using 100-face diagrams, where the affected proportion was coloured in to represent the percentage. The use of the same denominators, being 100 in this case, was applied in order to prevent confusion and to keep information balanced.

4.4.5. Components of the decision

Survival

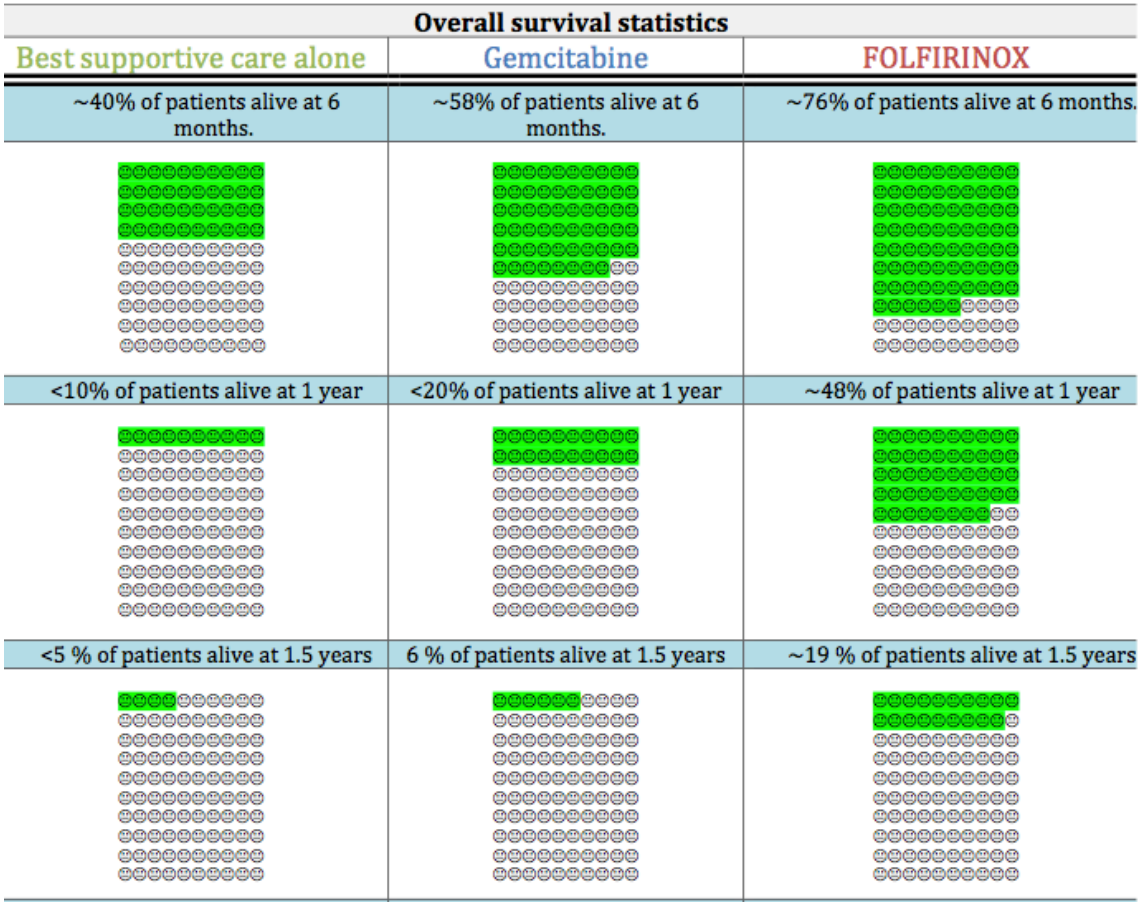
The first decisional component, survival, compares the treatment options in terms of the average length of time a patient may survive. The information on survival was divided into a superficial and more detailed description of the statistics, as some patients do not wish to know this information. By accessing the former option, patients would simply be advised that survival outcomes can be expected to be better if treated with chemotherapy treatment in comparison to best supportive care alone (Figure 12).

Figure 11: Comparison between chemotherapy and best supportive care alone for survival at a superficial level

What is most important to you?	No Chemotherapy-best supportive care alone (Observation and pain management)	Chemotherapy (Treatment with gemcitabine or FOLFIRINOX)
Survival *Increasing the length of time that I will live.*	-My chance of surviving longer is smaller when treated with best supportive care alone ☹	-My chance of surviving longer is greater when treated with chemotherapy ☺
	Best supportive care alone → Chemotherapy → Survival time	

A patient could also choose to access a separate link in order to learn the survival probabilities for each treatment option (Figure 13). Survival statistics are separate from the superficial comparison in order to protect patients who do not wish to know this information. Survival statistics were presented in periods of six-month blocks starting at 6 months and ending at 2.5 years to illustrate the proportion of patients alive at each time point. Survival rates were presented as percentages with both a numerical and visual representation of the statistic provided.

Figure 12: Comparison of overall survival rates between the treatment options for patients with advanced pancreatic cancer

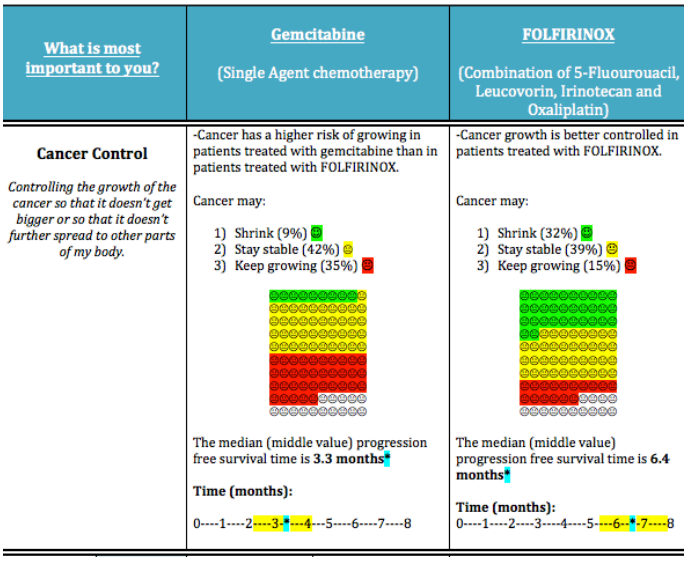


Cancer Control

The next component of the decision, cancer control, was presented to patients using similar methods that were used for presenting information about survival. The pros and cons of each treatment choice

were described in words, statistics and visual diagrams (Figure 14). The definition of cancer control was provided in the first column in order for patients to clearly understand the difference between cancer control and survival and interpret the statistics being shown to them correctly.

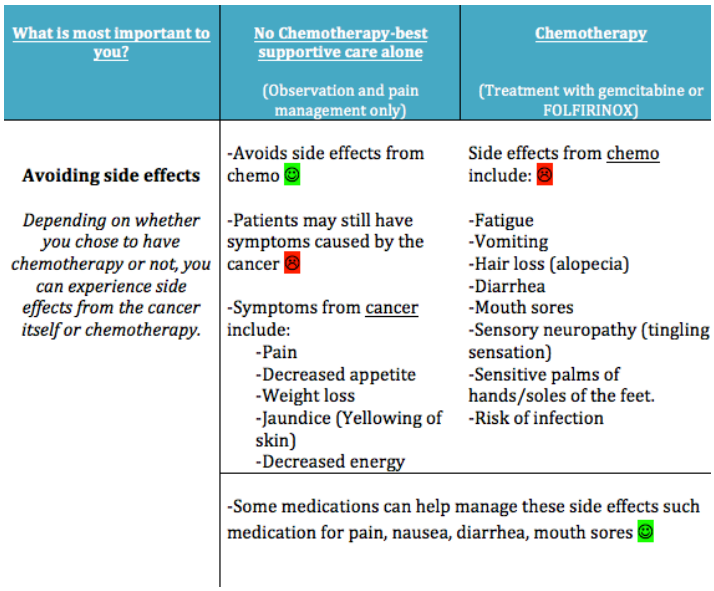
Figure 13: Comparison of cancer control rates between FOLFIRINOX and gemcitabine



Avoiding Side Effects

Information on side effects was then presented to patients, where the probabilities of a patient experiencing each grade 3 or 4 side effects were expressed in writing and visual diagrams (Figure 15). As side effects are caused by the chemotherapy treatment, patients were informed that by choosing not to be treated with chemotherapy, side effects from chemotherapy can be avoided.

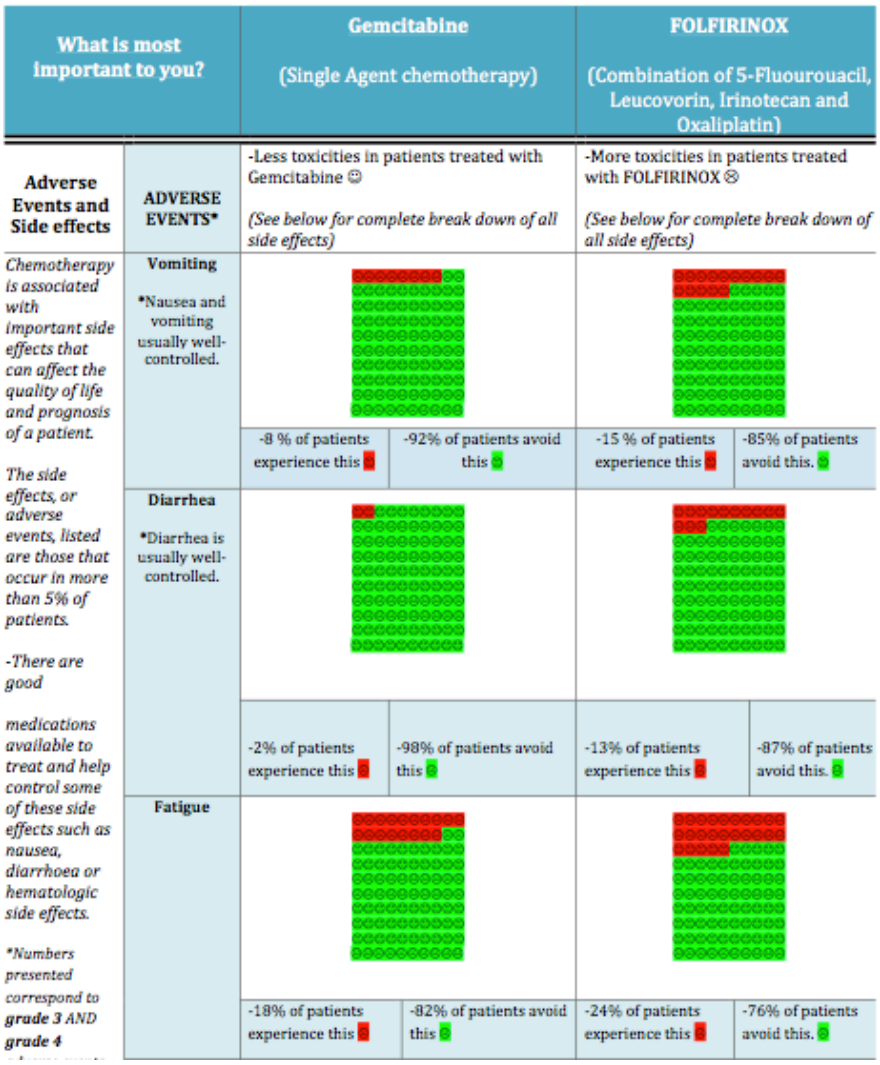
Figure 14: Comparison of side effects between chemotherapy and best supportive care alone



What is most important to you?	No Chemotherapy-best supportive care alone (Observation and pain management only)	Chemotherapy (Treatment with gemcitabine or FOLFIRINOX)
Avoiding side effects *Depending on whether you chose to have chemotherapy or not, you can experience side effects from the cancer itself or chemotherapy.*	-Avoids side effects from chemo ☺ -Patients may still have symptoms caused by the cancer ☹ -Symptoms from cancer include: -Pain -Decreased appetite -Weight loss -Jaundice (Yellowing of skin) -Decreased energy	Side effects from chemo include: ☹ -Fatigue -Vomiting -Hair loss (alopecia) -Diarrhea -Mouth sores -Sensory neuropathy (tingling sensation) -Sensitive palms of hands/soles of the feet. -Risk of infection
	-Some medications can help manage these side effects such medication for pain, nausea, diarrhea, mouth sores ☺	

A detailed description of the side effects associated with chemotherapy is presented in a separate link in order to prevent the risk of overwhelming the patient with information. The side effects selected to be reported included grade 3 or 4 vomiting, diarrhea, fatigue, sensory neuropathy, neutropenia, febrile neutropenia, anemia, elevated ALT, thromboembolism, and alopecia. The selection of side effects was based on findings in the literature, where the most commonly reported side effects were used.

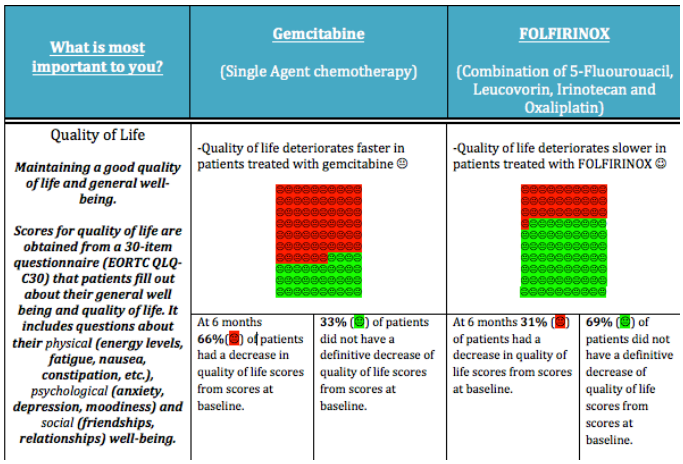
Figure 15: Excerpt of full list of the comparisons between FOLFIRINOX and gemcitabine for adverse events



Quality of Life

Quality of life was also compared between treatments as a statistic, where the proportion of patients with deteriorating quality of life was represented in red, and the proportion of patients who either have maintained or improved quality of life is coloured in green. An example is displayed in Figure 17. A definition of quality of life is provided in the first column, and details on the questionnaire used to determine the scores of quality of life is provided, as this can often vary from between clinical trials.

Figure 16: Comparison of quality of life between FOLFIRINOX and gemcitabine



Symptom Management

Patients are often confused with the difference between symptoms caused by the cancer itself and the side effects that are caused from the chemotherapy. By illustrating the distinctions between cancer related symptoms and chemotherapy related side effects, as well as highlighting the symptoms that a patient may experience that are exclusively caused by the cancer, such as jaundice, or pain, patients may better understand how chemotherapy may be able to treat cancer-related symptoms as it prevents further growth and ultimately help improve quality of life. Symptoms described were pain, fatigue, jaundice, anorexia-cachexia, and depression as they were the most commonly reported symptoms of pancreatic cancer (Figure 18).

Convenience

The length of time and number of treatment visits per regimen varies and can impact a patient's schedule. There may be associated costs of the treatment visits such as the cost of parking and transportation to and from the hospital and time off work, if applicable, must also be taken. Additional trips to the hospital such as imaging, blood work and follow-up visits may also increase the number of visits and length of time a patient spends at the hospital. Depending on the regimen, patients may stay for as long as five hours for the chemotherapy treatment which may or may not be inconvenient for

the patient, depending on if they are still working, if they have access to transportation services or if they have family or friends in the area that can bring them to their appointments. Furthermore, some treatments, such as FOLFIRINOX require a 48 hour infusion pump that a patient must carry with them after their treatment days. Patients must therefore adapt to being "hooked-up" to the pump for an additional two days, where they must sleep and carry on with their daily activities. Thus, for some patients, convenience may be an important factor in deciding on whether or not they chose to pursue chemotherapy treatment and which treatment they would prefer. By displaying the pros and cons of each, as well as a description of the treatment schedule including the number of visits, length of time of the treatment, and how many treatment cycles each option offers, a patient may grasp a better idea of what the associated costs and potential inconveniences may be in order to make a decision that best suits their preferences.

4.4.6. Clarification and expression of patient values

Going through the decision aid, patients are asked to consider which features matter most to them as well as communicate these values by rating the level of importance for each outcome of interest, on a scale from one to five, with five being most important (Figure 19). The descriptions of the positive and negative features of each outcome can be viewed while patients work through the decision aid and decide on how important each feature is. The presentation of the facts are readily available to the patients as they respond to questions about their values. The results from the importance scale are displayed as visual and numerical feedback at the end of the decision making process, so that patients can clearly understand their own prioritizations and rankings and share this information with others.

An example of feedback a patient received after responding the importance scale is shown in Figure 20. Below each importance scale for the different outcomes on the decision aid worksheet, patients are also asked to indicate on a scale from one to five how much they are leaning towards one treatment or the other, based on what they read or know about the treatment outcomes, and what their individual preferences are for that particular outcome. For example, for survival alone, patients who express survival as being very important to them may select a 4 or 5, indicating that they are leaning more towards chemotherapy. In contrast, a patient who strongly wishes to avoid side effects from chemotherapy, may lean towards best supportive care alone instead, selecting a 1 or 2, given that chemotherapy is associated with more side effects, based on the information they read on the

website. The same concept is applied to the FOLFIRINOX and gemcitabine decision aid comparing survival and safety outcomes for each feature of the decision. When considering each of the different features, patients are presented with objective, unbiased information for each comparison. The decision of whether a patient chooses one option over another is based on how they rate the importance of each outcome and which treatment they lean towards more in the end.

Figure 17: Excerpt of full list of comparisons between treatment options for symptom management

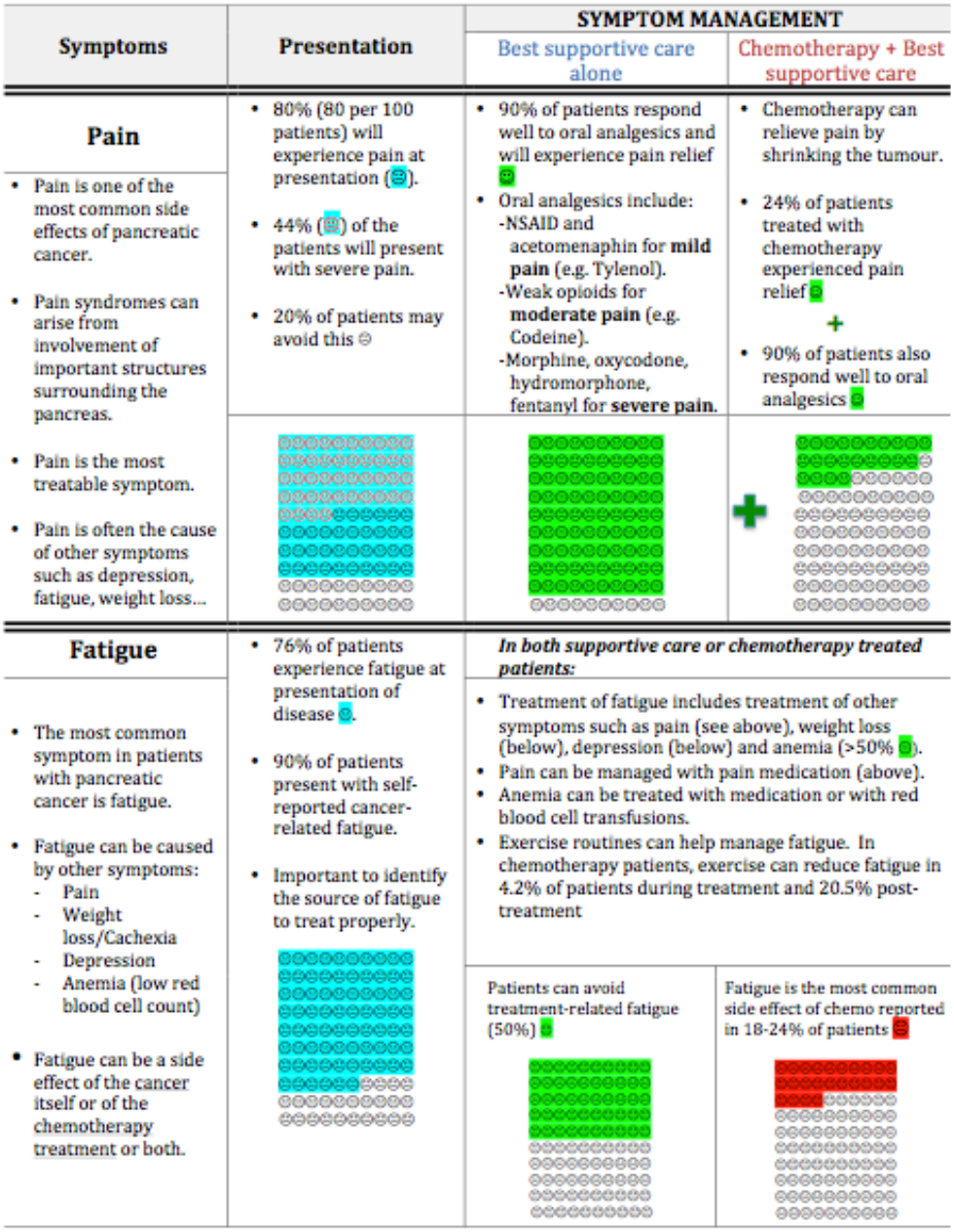
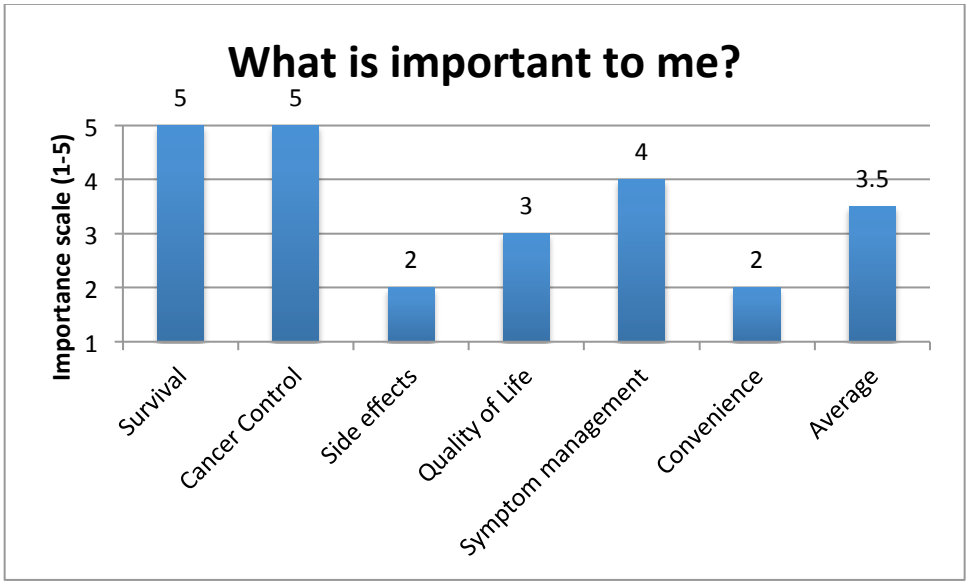


Figure 18: Screen capture of first step of the decision aid where patients are deciding between chemotherapy and best supportive care alone if survival was their only consideration

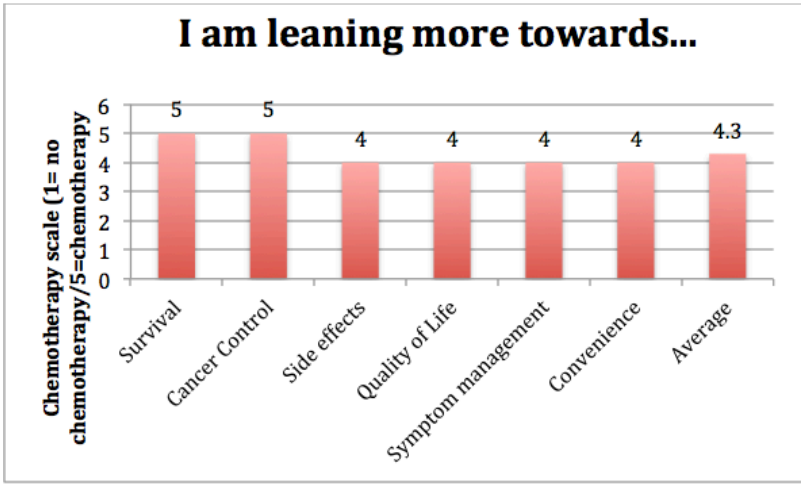
Figure 19 Feedback from the importance scale, as presented to patients, after completion of the decision aid, based on the six decisional components of the decision aid



4.4.7. Guiding the patient decisions

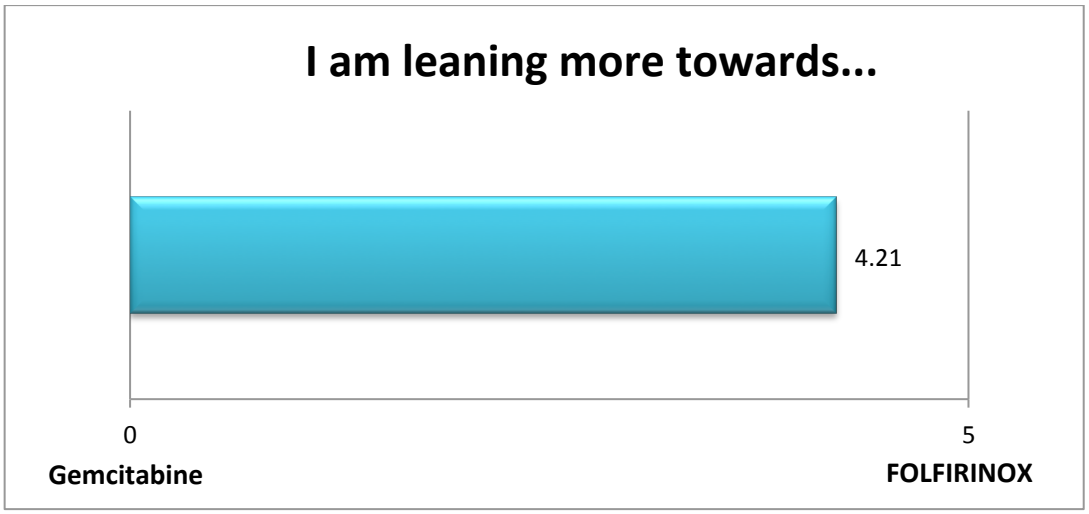
Once patients have completed the decision aid worksheets, they are provided with feedback of their overall ratings of each feature of the decision. It summarizes the importance scale as well as the chemotherapy decision scale (Figure 21). Taking the patient's values into consideration, further steps are provided to patients in order to make their decision. If survival, cancer control, symptom control and quality of life is very important to patients, and they are leaning more towards being treated with chemotherapy, patients will be guided to the next step of the decision making process: choosing between FOLFIRINOX and gemcitabine. Patients may also be interested in what others consider to be important and for which features other patients in their situation may lean towards one treatment over the other. An overall presentation of the patient's decision, based on an average of the patient's responses for each decisional component, is also provided to patients in the form of a bar graph on a scale from one to five (Figure 22).

Figure 20: Feedback from chemotherapy decision scale, as presented to patients after completion of the decision aid, based on the six decisional components



Based on your preferences and values, you are leaning more towards chemotherapy with an overall score of 4.3/5 (86%).

Figure 21: Mean value assigned to the overall decision between FOLFIRINOX and gemcitabine



**Mean value was calculated by adding the values assigned to each decisional component and dividing the total by six.*

4.5. Discussion

Patients who wish to participate in the decision-making process often seek information in other ways including searching the Internet or relying on testimonials. This can create unnecessary anxiety for the patients as well as false hope or unrealistic expectations. Furthermore, information found on the Internet may be misleading and not a reliable source of data for patients seeking updated and current knowledge to help with their decisions. A decision aid can provide high quality and relevant information about the benefits and risks that the treatments offer in a clear and comprehensible manner with an aim to assist patients in making informed decisions. The information provided in the decision aid is based on high-quality information in order to increase patient knowledge and understanding of relevant material. An internet-based design allows for easy modification and updates of information as it comes in, allowing the patient to always have access to the most current research. It also allows patients to access as little or as much information that they wish to view on their own time in the presence or absence of others.

The resulting decision aid was an interactive online tool that guided patients with pancreatic cancer through a step-by-step process that helped them identify their needs and prioritizations. By providing immediate feedback to the patient on their preferences and values in a visual manner, patients can easily print this out and present their results to their oncologist during the consultation. This information would be highly useful to the oncologist in learning what is most important to their patients and could help guide the final decision. The weigh scale exercise, which allows patients to quantify how much they are leaning towards one option versus the other, has been shown in other studies to predict the patient's final decisions with between 84-95% accuracy[39, 95,96].

By using an interactive, web-based format, patients are able to keep track of their answers, access several information pages at a time in order to properly answer each question they may have, and receive immediate feedback at completion of the decision aid questionnaire. Furthermore, the website design can protect patients from information that they do not wish to see, such as specific statistics about their prognosis. By including disclaimers and providing both the superficial and deeper level of information in separate links, patients can decide which information they wish to access.

4.5.1. Limitations

Although the use of an Internet-based format was mostly considered as an advantage to the design of this decision aid, some limitations surrounding its format still need to be addressed. One limitation was that there was a concern that not all patients may have access to computers or the Internet in order to use the decision aid. However, a survey conducted in 2010 reported that 80% of Canadians use the Internet[97]. In addition, a third of the population is also accessing the Internet on their mobile devices or portable tablets. Internet usage is still high amongst people within the target age group of the decision aid, where 80% of the population between 47-60 years, 51% of the population between 60-74 years, and 27% of the population 75 years and above uses the internet[97] and the median age of pancreatic cancer is 71 years. Also, 80% of the Internet users search health related topics, which next to email usage and search engines, is the most popular use of the Internet[97]. Most users search for information on specific health conditions or diseases (66%) or treatment procedures (56%). These Internet-usage

statistics thus support the design and development of an Internet-based decision aid for patients, where most patients will have access to the tool.

However, in order to reach the population of patients who may not have access, it was of interest to provide them with a paper-based version of this decision aid, in the form of an information booklet (Appendix 8). It will also be important to monitor the online use and compare the usage against incidence rates for advanced pancreatic cancer, to ensure that the complete target population is been captured.

Also, the introduction of a circulating IPad via hospital volunteers or access to the desktop computers in the waiting rooms would allow patients without Internet access, or other patients who are not comfortable using online decision aids at home, to complete the decision aid while waiting to see their doctor. At The Ottawa Hospital Cancer Center, computers are already set up in every module, as patients use them to answer the Edmonton Symptoms Assessment Scale (ESAS). If the decision aid were deemed to be acceptable in the pilot study, it would be of interest to allow eligible patients to access this link on the clinic's computer as well. This would not be difficult, as the symptom assessment scale currently completed by patients is accomplished through an Internet database where results can then be printed off in the clinic and provided to the oncologists in time for their visit with the patient. This concept inspired the idea of using the same system for patients using the pancreatic cancer decision aid, where they could complete the questionnaires in the waiting room and print out their feedback to bring to the medical oncologist during their consultation. This would allow the patients to communicate their values and preferences with their oncologist. It would further allow oncologists to identify the patient's prioritizations and offer a suitable treatment to the patient based on their needs.

4.5.2. Conclusion

By communicating the estimates of the likelihoods for different outcomes based on the best available evidence, and by displaying this in an objective, balanced manner using visual and numerical prompts this decision aid will allow patients to weigh the benefits and harms of each option and reach a decision based on their own values and without any influence. Next steps for the decision aid include its evaluation and appraisal. This would involve designing an intervention study at the pilot level that would evaluate the feasibility and acceptability of the decision aid, as well as identify the key elements

of the outcomes to learn such as the standard deviation that is required for determination of statistical significance. The pilot study would also be used to evaluate the impact of the developed clinical decision aid on patient knowledge and understanding of prognostic and treatment information, the realistic expectations, decisional conflict, and acceptance of the patient decision aid. Results from the study are presented in the subsequent chapter.

5. A NEEDS ASSESSMENT AND EVALUATION OF A PATIENT DECISION AID FOR ADVANCED PANCREATIC CANCER

5.1. Introduction:

Decision-making, where curative treatment is not an option, can be very complex and challenging. This is the case for patients with advanced pancreatic cancer-a devastating disease that kills 94% of the patients diagnosed with the disease each year[3]. Treatment options are limited, with no possible cure to offer and only modest survival improvements observed in even the most aggressive forms of treatment. Unfortunately, the more aggressive the treatment, the greater the risk of side effects and the question resurfaces of whether the risks are worth the marginal benefits that the treatment may offer.

In the advanced pancreatic cancer setting, several more aggressive forms of treatments have been introduced as gemcitabine based doublets or other forms of combination therapies, over the past couple decades, in effort to improve the grim survival rates. Over eighteen treatments were identified and compared with each other in a network meta-analysis to determine the optimal therapy and evaluate its safety in comparison to other treatments. FOLFIRINOX was found to be the most effective therapy for advanced pancreatic cancer with statistically superior overall survival and progression free survival rates in 15 out of 19 possible treatments. However, it was also found to be associated with significantly greater odds of developing grade three or four adverse events in comparison to gemcitabine alone. At the opposite end of the spectrum, gemcitabine, a single agent therapy, was associated with very modest survival improvement being ranked one of the lowest in the network meta-analysis, but also was found to be better tolerated amongst patients of all ages and performance statuses. Patients are therefore facing a difficult trade-off between survival for increased risk for side effects, which may or may not affect their overall quality of life. Despite the complexity of such a decision, no tools exist to guide patients with advanced pancreatic cancer through this decision making process. The decision between treatments for advanced pancreatic cancer requires careful consideration and understanding of all aspects of the decision making process. A clear understanding of the advantages and disadvantages associated with all of the important endpoints including survival,

cancer control, symptom management, quality of life, avoiding side effects or convenience is crucial for the patient's active participation in the decision-making process.

With the objective of properly informing patients of the benefits and risks that each treatment for advanced pancreatic cancer offers, including the option of no active treatment, a patient decision aid was developed and presented to patients to determine its acceptability and feasibility in a small pilot study.

5.2. Objectives

A pilot study of the decision aid was conducted with the primary objectives of determining the needs for a decision tool and testing its overall feasibility and acceptability. It was hypothesized that the format and mode of delivery of the decision aid would be acceptable and that the decision aid would improve patient's overall knowledge of the disease and treatment options while decreasing decisional conflict.

5.2.1. Methods

5.2.2. Study design

With ethics approval from the Ottawa Hospital Research Ethics Board (OHREB), a single-center, single arm prospective observational study was conducted at The Ottawa Hospital Cancer Center between March 15th and April 30th, 2013. The pilot study was conducted with the primary objective of assessing decision aid feasibility and acceptability, as well as looking at patient knowledge and decisional conflict scores in a descriptive manner.

All medical oncologists in the region who treated patients with pancreatic cancer agreed to refer patients to the study and accepted responsibility for determining patient eligibility.

5.2.3. Inclusion/exclusion criteria

Male and female patients aged ≥ 18 years at time of study enrolment were recruited into the study. It was essential that patients were aware of their diagnosis of pancreatic cancer and understood that it had spread and was not curable. If patients met this baseline criteria, they would then be further included if they provided written informed consent; were histologically confirmed to have an adenocarcinoma of the pancreas; had an ECOG PS of 0-2, and were being seen for their first medical oncology consultation at The Ottawa Hospital Cancer Center. Patients were required to be anti-cancer treatment naïve with the exception of surgical procedures and radiation for palliation. Excluded were patients who were unaware of their diagnosis of pancreatic cancer, or uncertain about whether the cancer had spread, and if they had been previously treated with chemotherapy or radiotherapy for advanced pancreatic cancer.

5.2.4. Administration of the decision aid

There were two principal approaches used to identify and recruit patients. The approach selected depended on whether the patient was first being seen by the surgical staff, or whether the patient was triaged directly to the nursing staff that was responsible for scheduling the patient's appointment the medical oncologist.

In the circumstance of a patient being identified with stage IV pancreatic adenocarcinoma through the hepatobiliary surgery clinic, the surgical oncologist and/or the intake nurse in the hepatobiliary clinic asked the patient if they were willing to be contacted for a study. If the patient agreed, the research associate was then responsible for contacting the patient to arrange a meeting to discuss the study and obtain informed consent.

In the instance that a patient was referred directly to the medical oncologist, which occurred more frequently, due to the lower rate of unresectable disease determined during surgery in the hepatobiliary clinic, the registration intake nurse at the cancer center would notify the medical oncologist of the incoming patient. The medical oncologist was subsequently responsible for reviewing the patient's chart in advance in order to determine the patient's eligibility, and if the patient was

eligible, introducing the patient to the study. The medical oncologist could contact the patient by phone or in person at an appointment occurring prior to their consultation. If a patient agreed to participate in the study, the research associate would then be contacted and would go through the informed consent process with the patient and obtain their signature. The information and consent form was available in both English and French, and can be found in Appendix 9. A complete script of the informed consent process by telephone can be found in Appendix 10. The ethics board approval letter is included in Appendix 11.

Consenting patients who are scheduled to be seen at The Ottawa Hospital Cancer Centre (TOHCC) by a medical oncologist for their diagnosis of metastatic pancreatic cancer were provided the URL to the decision aid website as well as an accompanying pamphlet which encloses all the information and questionnaires that can be found on the website. They were required to complete the "Patient Knowledge" questionnaire at the time of their enrolment into the study and then were given time to use the decision aid prior to their chemotherapy consultation visit with the medical oncologist. It could be delivered within a week before or on the same day of consultation. The online website includes information on pancreatic cancer, on the treatment options available for their diagnosis and on the two decisions that the patient will be making: 1) Chemotherapy + Best supportive care vs. Best supportive alone; 2) FOLFIRINOX vs. Gemcitabine. This was accomplished either on a circulating study I PAD or on the patient's home computer, if applicable.

5.2.5. Needs assessment

The Ottawa Decision Support Framework served as the framework for assessing decisional needs amongst practitioners and patients. Following this framework, the decision type, timing stage and leaning; personal/clinical characteristics; decisional conflict; knowledge, expectations; values perceptions of others; social pressure and lack of support were evaluated using questions that address each of these components. The last two components of the decisional framework, lack of skills/self-confidence and lack of other resources, were omitted for the purpose of this study, as they were felt to be less applicable to the study population and it was decided that they would not provide a strong

basis for decisional needs. All questions were adapted from a standard template for addressing decisional needs based on the Ottawa Decision Support Framework[39,98,99].

The needs of a decision aid was also determined amongst the medical oncologists who would be responsible for administering such a tool in the clinic, should it be accepted as common practice. Thus, it was important to determine the optimal time to distribute the decision aid, the best format, and what the target population would be. The questionnaire was divided into two parts, where physicians were asked to complete a 9-item questionnaire prior to the consultation with their patient which asked questions about the physician's practice characteristics (specialty, number of years practicing their specialty, etc.) and what role they play in the decision-making process with their patient, whether they believe a decision aid would be useful, and what barriers they believe patients may face when making their decision. This questionnaire was adapted from the standard template for eliciting needs base provided through the Ottawa Decision Aid Support Framework[39]. The questionnaire included multiple choice and open-ended questions with probes. The open-ended questions were adapted to apply to pancreatic cancer, where physicians were asked whether there was a specific patient population they would or would not recommend gemcitabine or FOLFIRINOX to and what factors prevented them from suggesting chemotherapy to a specific population.

5.2.6. Decision Aid Outcomes

Main outcomes used to evaluate the patient decision aid, for the purpose of this small pilot study, were feasibility and acceptability. These outcomes were selected based on the Ottawa Decision Support Framework, where validated tools exist to measure and test these outcomes. The first outcome, feasibility was used to measure the patients overall satisfaction with the decision that they made and how useful the patient decision aid was in making this decision and how it helped them recognize there was a decision to be made (APPENDIX 12). The answer options for each of the ten questions on the questionnaire were "Not at all"; "A little"; "Somewhat"; "Quite a bit" and "A great deal." Patient response to either "Quite a bit" and "A great deal" were assigned a score of 1, "somewhat" was assigned a 0, and "Not at all" or "A little" were assigned scores of -1. The total amount of points for the questionnaire was 10, where a score greater than 8.5/10 would be deemed

feasible, decided *a priori*. The second outcome, acceptability, was also assessed using a questionnaire, based off of the OCDS acceptability questionnaire and adapted to include questions that specifically address the acceptability and usability of Internet-based decision aids in order to apply to the design of this particular decision aid. Thus, additional questions pertaining specifically to the ease of navigation, usability and requirement of support in order to use the online tool were asked. Patients were also asked to evaluate the content of the decision aid, the quantity and quality of information presented and the helpfulness of the decision aid itself. Questions were presented in a ten-item decision aid acceptability questionnaire (Appendix 13). A point value for each answer option for the ten questions included in this questionnaire was assigned where the maximum amount of points the patient could receive was 10, and each percentage was converted into a fraction of 1 (value of 100=1 point, 75=0.75 points, 50=0.5 points, *etc.*) and these were added up based on the assigned point value for each answer. Each questionnaire was estimated to take between ten to fifteen minutes to complete. With access to the questionnaires online, patients could complete the questionnaires on their own time at home or in the waiting room. The decision was deemed to be acceptable and feasible if the mean score amongst patients for each questionnaire was greater than 85%, which was decided *a priori* and based on a clinical expert recommendation.

Other outcomes that were measured to assess the needs basis for this decision aid included patient knowledge and decisional conflict, which were distributed to patients prior to the distribution of the decision aid. Patient knowledge encompasses all general knowledge and retention of information about the disease, the treatment options available, and the associated adverse effects and benefits of the respective treatments. A valid and reliable scale has been designed to measure this outcome[99]. The knowledge test was adapted to include questions specific to the disease of interest and its associated treatment options. The patient knowledge and expectations tool was designed as a ten-item questionnaire that tested the patients understanding and knowledge on pancreatic cancer and on general and more specific information on gemcitabine, FOLFIRINOX and some survival probabilities. The questionnaire is included in Appendix 14. For the purpose of this pilot, it was of interest to determine the baseline level of patient knowledge and the acceptability of the knowledge test. A mean score <50% would indicate that questions were too difficult, and a baseline score >80% would indicate that questions were too easy. Using patient baseline knowledge scores, the test could then be

modified and improved for the use of the second step of a pilot study where patient knowledge is being compared before and after the distribution of the decision aid. The second outcome, decisional conflict, was tested in order to describe how well-informed patients feel about their choices and the associated benefits and risks, the clarity of their values, the support they had in the decision-making process and their level of uncertainty around their decision[100]. A validated and reliable scale exists to assess decisional conflict, which was referenced from the Ottawa Decision Aid research group website[96]. The Decisional Conflict questionnaire was adapted as a sixteen-item questionnaire that addresses all aspects around the patient's confidence in the decision that they made and the role the decision aid played in their decision. It also explores the role of the family and physician in the decision. Finally, patient satisfaction with their decision and their overall perception of acceptability of the tool was measured using a subscale of the decisional conflict scale.

5.2.7. Data collection

All questionnaires were web-based and linked to the online decision aid. Thus, patient answers were automatically recorded in excel sheets for the needs assessment, knowledge, decisional conflict, acceptability and feasibility questionnaires. Additional data such as patient characteristics were collected from the patient medical records. Information collected included patient gender, year of birth, maternal language, marital status and whether they had kids. Information on disease characteristics such as the extent and location of spread was also recorded.

5.2.8. Statistical analysis

Descriptive statistics were employed to describe patient and physician characteristics. Frequencies of demographic factors such as age, sex, marital status and number of offspring as well as social economic status and disease characteristics were reported. The primary objective of this pilot study was to summarize the patients' quantitative perceptions of the decision to be made, their overall expectations and knowledge of the disease and treatment options available to them, and their attitudes towards the use of the patient decision aid. This was accomplished by calculating the frequency of responses to each question answered by patients in the patient knowledge, decisional conflict and acceptability

questionnaires. All patient responses were reported as percentages. Mean scores, the mean ranks, and their standard deviation were calculated for each of the questions. Statistical analyses were performed using SAS version 9.3 (SAS Inc, Carey, NC, USA).

5.3. Results

5.3.1. Study participants

Four consenting patients were included in the pilot study. There were 2 females (50%) and 2 males (50% male) with advanced pancreatic cancer disease considering chemotherapy. Patient characteristics are denoted in Table 6. Two patients presented with disease that had spread locally and deemed unresectable, while the remaining two (50%) patients had metastatic disease to the liver or lungs. Self-reported ECOG performance status was 0 and 1 for 25% and 75% of patients, respectively.

Table 6: Baseline characteristics of patients piloting the chemotherapy decision aid

Baseline characteristics		N	%
Gender			
	Male	2	50
	Female	2	50
Age			
	20-50	1	25
	50-70	0	0
	70-80	1	25
	80-90	1	25
	90-100	1	25
	Median	85	(range 46-90)
Site of metastases			
	Liver	1	25

	Lung	1	25
	Lymph Nodes	1	25
	Pancreas	1	25
Previous resection			
	Yes	1	25
	No	3	75
Married			
	Yes	1	25
	No	1	25
	Widowed	2	50
Offspring			
	Yes	3	75
	No	1	25
Maternal language			
	English	3	75
	French	0	0
	Other	1	25
ECOG			
	0	1	25
	1	3	75
	2	0	0
	3	0	0

5.3.2. Needs assessment

5.3.2.1. Practitioner needs assessment

Four physicians who treat pancreatic cancer at The Ottawa Hospital Cancer Center and were not involved in the design or development of the decision aid completed the questionnaire. Practitioner characteristics are outlined in Table 7.

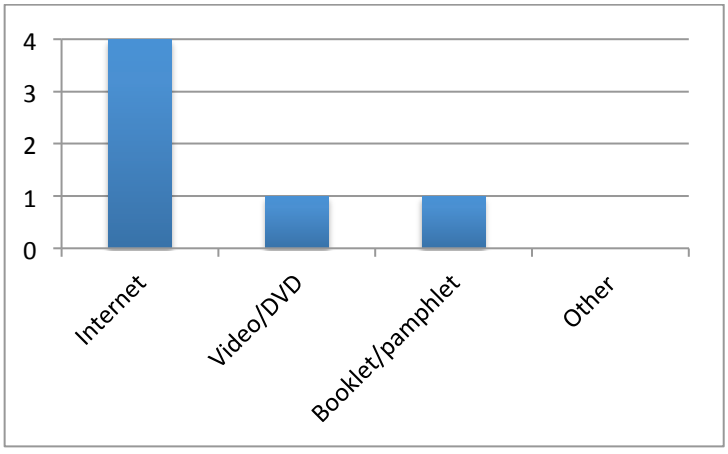
Table 7: Characteristics of medical oncologists treating advanced pancreatic cancer at TOHCC

Practicioner characteristics		N	%
Gender			
	Male	1	25
	Female	3	75
Age			
	20-30	0	0
	30-40	1	25
	40-50	2	50
	50-60	0	0
	60+	1	25
Years of practice			
	0-5	2	50
	5-10	1	25
	10-20	0	0
	20+	1	25
First language			
	English	3	75
	French	1	25

	Other	0	0
Practitioner's role in decision making			
	Makes the decision for the patient	0	0
	Shares the decision with the patient	2	50
	Provides advice and support so patient can make decision on their own	2	50

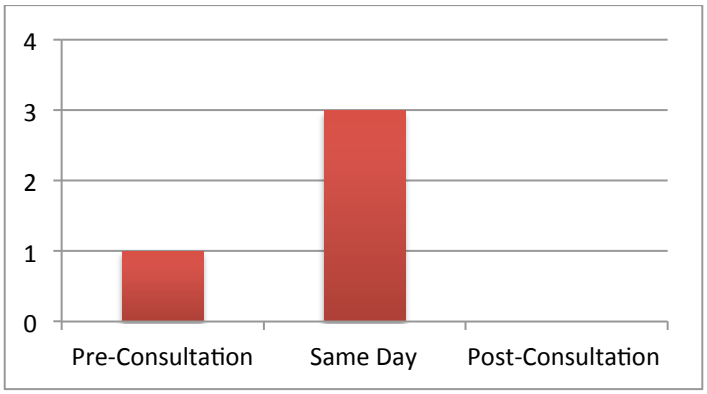
All of the physicians (4/4) responded that a decision aid would be useful for this population of patients, where the majority of physicians answered that an Internet-based decision aid would be the best format. One physician suggested that pamphlet that accompanied the Internet decision aid may be useful. Another physician also recommended the use of a video or DVD (Figure 23). Physicians recommended that the optimal time for distribution of a decision aid to be the same day of consultation (Figure 24).

Figure 22: Suggested format for decision aid according to physicians



**More than one answer could be selected for this question.*

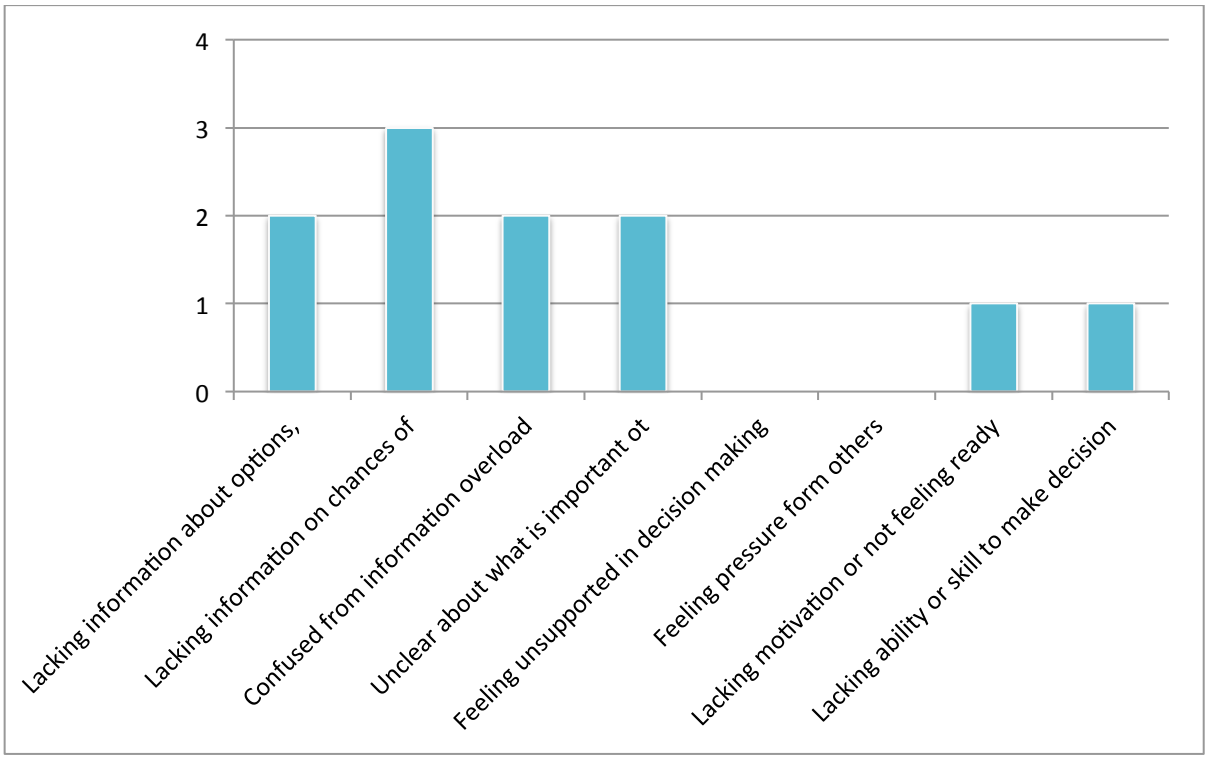
Figure 23: Optimal time for distribution of decision aid according to physicians



**More than one answer could be selected for this question.*

Physicians identified the lack of information on chances of benefits and harms to be the greatest problem patients face when making the decision (27%) (Figure 25). Lack of information about options (18%), benefits and risks (18%), confusion from information overload (18%) and lack of clarity of what is important to patients (18%) were also leading factors that physicians believed made the decision more difficult for patients. Other factors that physicians selected included lack of motivation (9%) or not feeling ready to make the decision and the lack of ability or skill to make the decision (9%). None of the physicians thought that patients felt unsupported in the decision-making process or felt pressure from others. The majority of physicians (71.4%) would not recommend any chemotherapy to patients with poor performance status (ECOG PS >3) and 28.6% would not recommend it to the elderly or frail. For FOLFIRINOX, 71.4% of physicians would not recommend FOLFIRINOX to patients with poor performance status, 14.3% would not recommend it to frail patients, and 14.3% would not recommend it to elderly patients.

Figure 24: Practitioner's perception of patient barriers to decision making



**More than one answer could be selected for this question.*

5.3.2.2. Patient needs assessment

Patient needs were assessed based on the Ottawa Decision Support Framework, where the decision type, timing, stage; patient characteristics; decisional conflict; lack of knowledge; unrealistic expectations; unclear values; unclear perceptions of others; social pressure and lack of support were used to evaluate patient needs (Table 8).

Decision type, timing and stage

Based on the ODSF decisional needs criteria, the stage of the decision addressed in this decision aid is "Actively deliberating" where patient's decisional conflict and uncertainty is high and decision support is "most helpful".

Patient characteristics

The second decisional needs component, following the ODSF, was then considered. The decision aid was designed for both males and females as there is an even distribution between males and females in this population, and accommodates the person's physical, emotional and cognitive capacities. It also addresses patient educational background, where the average reading score of the entire decision aid was grade 8.17, deemed acceptable by ODSF, and allows patients from all educational backgrounds can understand the decision aid. Furthermore, accompanying diagrams and drawings can increase its comprehensibility.

Table 8: Decisional needs components, definition and patient ratings from decisional needs questions

Decisional Need	Definition (OSDF)	Mean Patient Score (value/total)	%
Knowledge	Lacking knowledge about the options and potential outcomes of options	11.5/18	64
Realistic expectations	Unrealistic expectations or perceptions of the likelihood of outcomes, such as exaggerating or minimizing the chances of outcomes	1/1	100
Clarity of values	Unclear values or unclear about what is most important	3.7/5	74
Clarity of perceptions of others	Unclear perceptions of others (doctor/family) including opinions and practices	4/5	80
Social Pressure	Social pressure from family/doctor/friends to choose an option	3.7/5	74
Support in decision process	Lack of support or mismatch between preferred and actual role in decision making	3/5	60
Decisional conflict	Uncertainty about which course of action to take when making a choice	3/5	60

**The higher the score, the better the outcome where the highest possible score beign 100*

Lack of knowledge

To determine whether there was a need for a decision aid in terms of patient knowledge about options and the potential outcomes of options, a ten-item knowledge test was administered prior to the distribution of the decision aid. A summary of the knowledge scores can be found in Table 9. The average score was 11.5 out of 18 possible points (64%), and both the median and mode was 12 out of 18 (62.7%). All patients (100%) responded that they were unaware of their treatment options prior to using the decision aid.

Table 9: Overall results of patient baseline knowledge test where a maximum of 18 points could be awarded

Patient	Points (/18)	Score (%)
1	9	50
2	12	66.7
3	12	66.7
4	13	72.2
Average	11.5	64
Median	12	66.7
Mode	12	66.7

Table 10: Patient decisional needs assessment based on knowledge of treatment options

Were you aware of the different treatment options available to you before using this decision aid?	Answer options	Patient responses (%)
	Yes	0
	No	100
	Unsure	0

Unrealistic expectations

Patients were also asked about their expectations from the treatment, where they were asked whether treatment would cure their disease. All patients (100%) responded correctly to this question. One patient commented, *"The side effects for gemcitabine aren't as bad as I thought they would be."*

Unclear Values

Patients were asked whether they were clear about what was important to them, where the mean score was 3.7/5.

Social pressure

Patients were asked about how strongly they agreed that they were making their decisions without pressure from others such as the doctor family or friends. The calculated mean score on a scale from one to five was 3.7.

Lack of support

Lack of support was evaluated by asking patients how strongly they agreed, on a scale from one to five, that they had enough support to make their decision. The mean score for this response was 3 out of 5 (60%).

Decisional conflict

Patient uncertainty about which course of action to take when making a choice, was evaluated using a scale from one to five, where the mean score was 3/5 (60%).

5.3.2.3. Decision aid results: Patient values

Four patients completed both steps of the decision aid. Before answering the chemotherapy decision scale, patients were asked what was most important to them in terms of survival, cancer control, avoiding side effects, quality of life, symptom management and convenience. For the importance scale, survival and cancer control were "very important" to 75% of patients, while 25% of patients answered

them as being “somewhat important”. Avoiding side effects was very important to 50% of the patients; “somewhat important” to 25% of patients and the remaining 25% responded “. For quality of life, 50% of patients selected “very important, 25%, “somewhat important” and 25% were unsure. Symptom management was divided into 75% of patients answering “very important” and 25% as “somewhat important.” Finally, for convenience, 25% said it was “very important,” 25% thought it was “somewhat important,” 25% were unsure, and 25% thought it was somewhat unimportant. No patients answered “Not at all important” for any of the decisional components.

Survival, Cancer Control and Symptom Management had the highest mean scores on the importance scale of one to five, with a mean value score of 3.75 for each (Figure 27). Avoiding side effects was the second most important decisional component with a mean score of 4.25, followed by quality of life with a mean score of 4 and lastly, convenience, with a mean score of 3.75.

Figure 25: Distribution of patient responses for the importance scale for each decisional componen, as a percentage

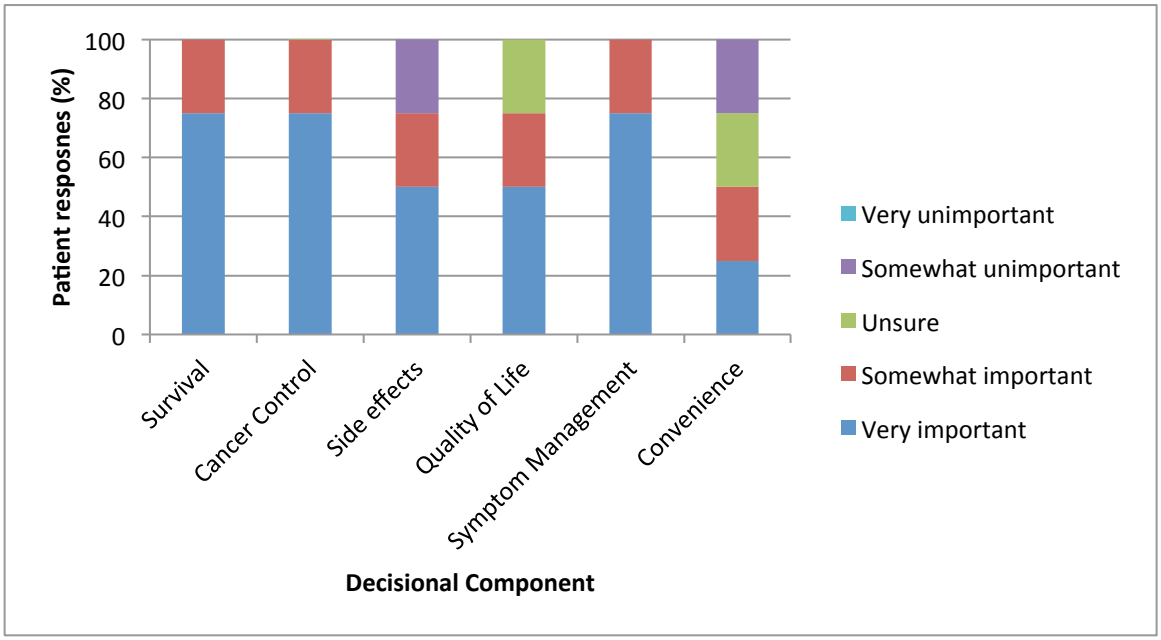
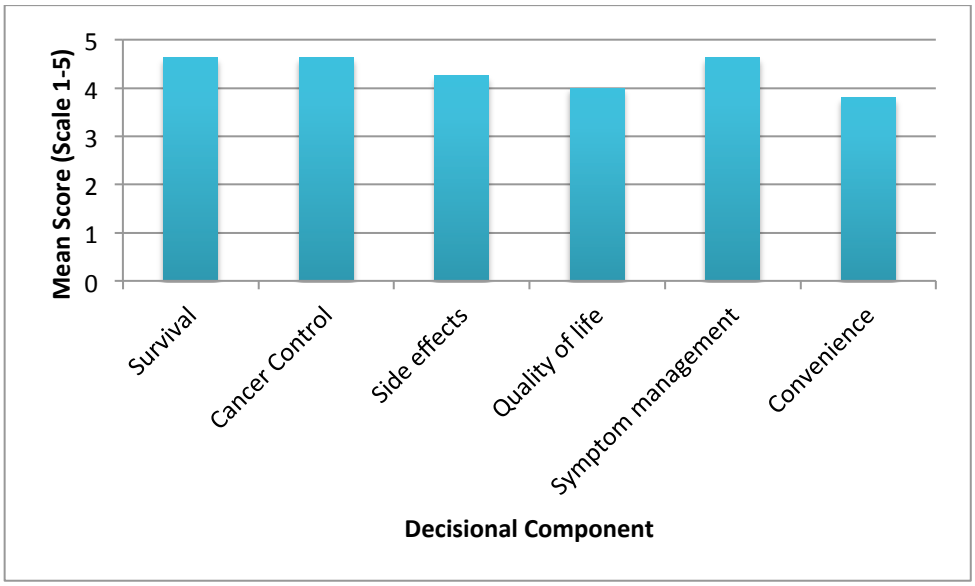


Figure 26: Mean score on the patient importance scale for each of the decisional component



5.3.2.4. Decision aid results: Decision between chemotherapy and best supportive care alone

The first decision was divided into six decisional components where patients were asked based on how important each component was to them, and if that particular component were their only consideration, which treatment they would be leaning towards. Based on their answers, 50% of the patients would "maybe" choose chemotherapy, 25% of patients were unsure, and the remaining quarter would "definitely choose chemotherapy," if survival was their only consideration (Figure 28). If cancer control were a patient's only consideration, half (50%) the patients would definitely choose chemotherapy while the other half (50%) were unsure. When patients were presented with statistics about avoiding side effects, half of the patients were unsure again while the other half answered "maybe." For both quality of life and symptom management, 50% of patients selected maybe and 50% selected unsure. For convenience, 25% of patients who had rated convenience as very important selected "definitely no," 25% selected "unsure" and 50% selected "maybe." The mean scores for survival, cancer control and side effects were all 4, while quality of life and symptom management were 3.5 and convenience was 3 (Figure 29). The mean score for the overall decision for patients,

where 5 indicated that patients were leaning more towards chemotherapy and 1, towards best supportive care alone, was 3.7 out of 5 (74%) (Figure 30).

Figure 27: Percentage of patient responses to various decisional components included in the first step of the decision aid where patients are choosing between chemotherapy or best supportive care alone for each of the different components of the decision

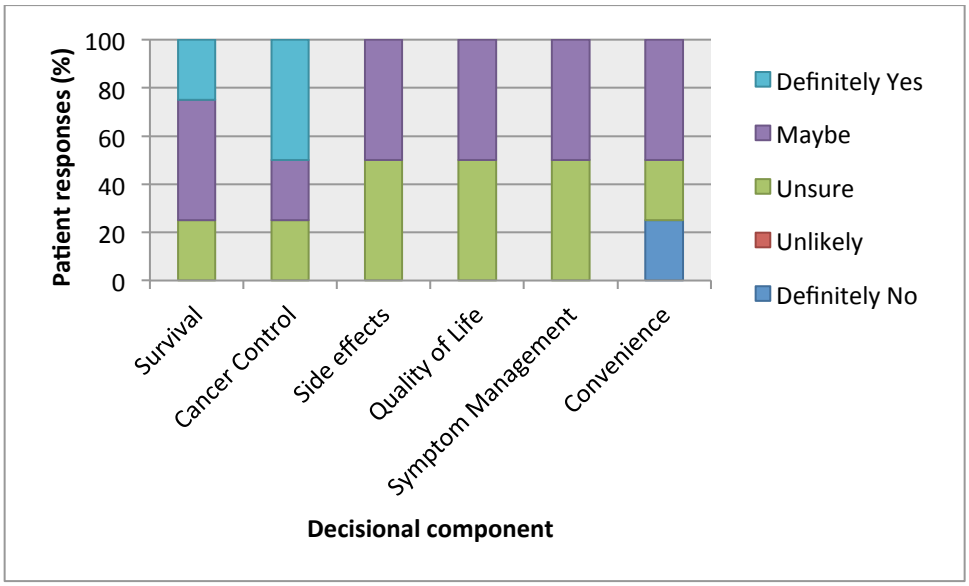


Figure 28: Mean scores for each decisional component and for the overall decision based on patients responses for the chemotherapy and FOLFIRINOX decision aids

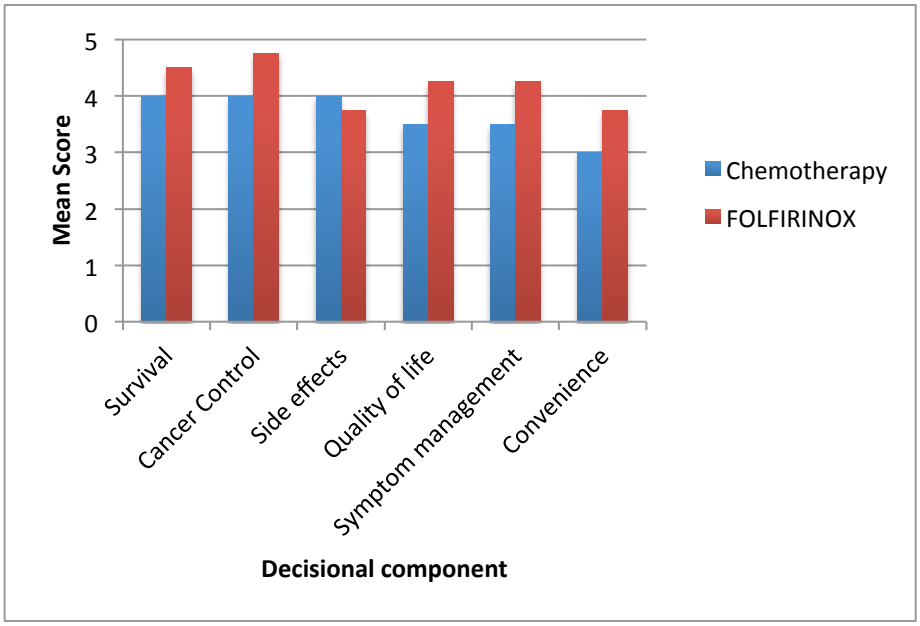
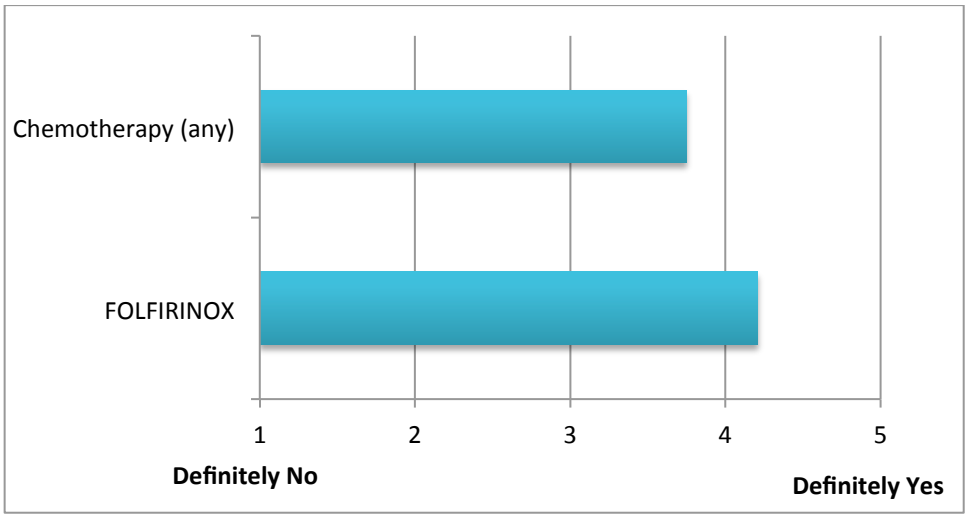


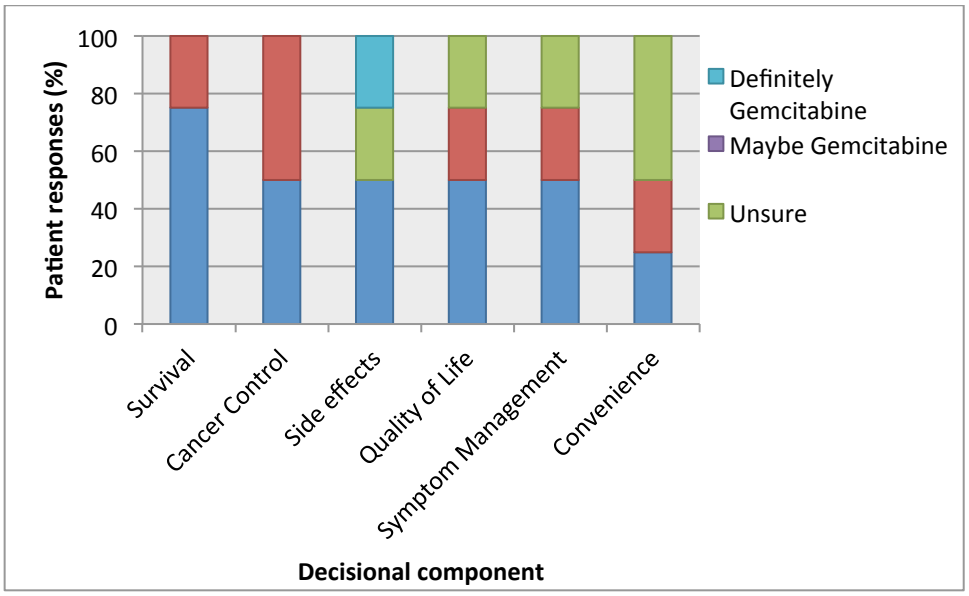
Figure 29: Mean scores for the overall decision for chemotherapy and FOLFIRINOX



5.3.2.5. Decision aid results: Decision between gemcitabine and FOLFIRINOX

Patients were guided through the same questions in the second part of the decision aid, where patients are deciding between either gemcitabine or FOLFIRINOX (Figure 31). If survival was their only consideration, 75% of patients would chose FOLFIRINOX with a mean score of 4.5 out of 5 possible points. The other quarter would chose “maybe FOLFIRINOX” while 0% were unsure or leaning towards gemcitabine. For cancer control, half the patients “definitely FOLFIRINOX” and the other half, “maybe FOLFIRINOX.” The mean score was 4.75 out of 5 (Figure 29). When considering side effects, half the population selected “definitely FOLFIRINOX,” a quarter was unsure and the remainder selected “definitely Gemcitabine.” The mean rank for this decisional component was 4. For quality of life, the mean score was 4.25 and half the patients selected “Definitely FOLFIRINOX,” 25% selected “Maybe FOLFIRINOX,” and the remaining 25% were unsure. Similarly, for symptom management, 50% of patients selected “definitely FOLFIRINOX”, a quarter selecting “maybe” and the rest selecting “unsure”. The last component, convenience, was divided into a quarter of patient responses being “definitely,” 25%, “maybe,” and 50% “unsure”. The mean score was 3.75. Finally, the overall score for the decision between FOLFIRINOX (5) and gemcitabine (1) on a scale from one to five, was 4.21 (84.2%) (Figure 30).

Figure 30: Percentage of patient responses to various decisional components included in the second step of the decision aid where patients are choosing between chemotherapy or best supportive care alone for each of the different components of the decision



5.3.3. Decision aid acceptability

Results from the decision aid acceptability questionnaire are outlined in Table 11. All patients (100%) felt that the use of an Internet-based decision aid was acceptable, where 75% had answered that the use of an Internet-based decision aid had a positive effect on them while the remaining 25% preferred the computer based decision aid, but required assistance. All patients responded that the decision aid was not difficult in terms of navigation around the pages and accessing the desired information. The amount of information was considered to be "just right" for all patients and the quality of information provided in the decision aid's information pages were all rated as either very good or excellent, where the complete break down of the ratings of information quality can be found in Table 11. All patients (100%) would recommend the decision aid to others. The majority of patients went through the decision aid with a member of the healthcare staff (75%) although 25% had used the decision aid on their own at home as well (Table 12). The decision aid took between 0-3 hours to go through and answer all questions. The overall acceptability score for the 10 questions of the acceptability scale was 90%.

Table 11: Decision aid acceptability: Patient answers to acceptability questions

Questions	Options (point value)	% responses
Question 1: How did the computer based decision aid affect you?		
	Positive effect (1)	75
	Negative effect (-1)	0
	Neither positive nor negative effect (0)	0
	I preferred using a computer but needed someone to help me navigate through the website (0)	25
	Overall score	0.75/1
Question 2: How difficult was it for you to navigate this website and find the information you were looking for?		
	Not difficult at all (1)	100
	Somewhat difficult (0)	0
	Very difficult (-1)	0
	Overall score	1/1
Question 3: Information provided on pancreatic cancer was		
	Poor (-1)	0
	Fair (-1)	0
	Good (0)	0
	Excellent (1)	100
	Overall score	1/1

Question 4: Information on treatment options was		
	Poor (-1)	0
	Fair (-1)	0
	Good (0)	0
	Excellent (1)	100
	Overall score	1/1
Question 5: Information on the benefits associated with each type of treatment was		
	Poor (-1)	0
	Fair (-1)	0
	Good (0)	25
	Excellent (1)	75
	Overall score	0.75/1
Question 6: Information on the risks and side effects of the treatment options was		
	Poor (-1)	0
	Fair (-1)	0
	Good (0)	25
	Excellent (1)	75
	Overall score	0.75/1
Question 7: The decision aid for choice of chemotherapy vs. best supportive care alone was:		
	Poor (-1)	0
	Fair (-1)	0
	Good (0)	25
	Excellent (1)	75

	Overall score	0.75/1
Question 8: The decision aid for choice between FOLFIRINOX and gemcitabine was:		
	Poor (-1)	0
	Fair (-1)	0
	Good (0)	0
	Excellent (1)	100
	Overall score	1/1
Question 9: The amount of information included in this website was:		
	Too little information (-1)	0
	Too much information(-1)	0
	Just right (1)	100
	Overall score	1/1
Question 10: Would you recommend this educational tool and decision aid to others that face the same treatment options?		
	Yes (1)	100
	Maybe (0)	0
	No (-1)	0
	Overall score	1/1
Total score		9/10

Table 12: Patient responses for overall usability of the decision aid

Questions	Answer options	% responses
How much time did you spend going through the decision aid?		
	0-3 hours	100
	3-6 hours	0
	More than 6 hours	0
	Not sure	0
How did you divide your time when using the decision aid?		
	Went through the decision aid all in one sitting/one day	75
	I spent a little bit of time going through the decision aid every day	25
	Not sure	0
Did anyone help you use the decision aid?		
	No-I went through this myself	25
	Yes-a family member helped me	25
	Yes- a friend helped me	0
	Yes- a member of the healthcare staff helped me	50

5.3.4. Decision aid feasibility

A complete list of patient responses to the feasibility questionnaire is outlined in Table 13. Overall, 75% of patients answered “A great deal” for the first four questions that asked if the educational material

had helped them recognize that a decision needs to be made; helped prepare them to make a better decision; help them think about the pros and cons of each decision and help them think about which pros and cons were most important to them. The remaining 25% of patients had answered “Quite a bit” for each of these questions. The fifth question, which asked whether the material helped them know that the decision depends on matters most to the patients, was answered “Quite a bit” for 75% of the patients and “A great deal” for 25%. Next, the educational material helped 100% of patients organize their own thoughts about their decision in question six. Half of the patients answered “A great deal” while 25% answered “Quite a bit” and 25% answered “Somewhat” when asked if the educational material helped them decide how involved they wanted to be in the decision. Next, patients were asked if the educational material helped them identify which questions they wanted to ask their doctor, where 75% answered “A great deal” and 25% answered “Somewhat.” Second to last, 75% of the patients thought that the decision aid helped prepare them to talk to their doctor about what matters most to them “A great deal”, and 25% thought it helped them “Quite a bit.” Finally, all patients agreed that this decision aid helped them to prepare to share the decision making process with their doctor.

To test the objectivity of the decision aid, patients were asked whether they found the information presented to them to be slanted or to be balanced. All patients (100%) responded that the decision aid was found to be objective and balanced when presenting the different treatment options (Table 14).

Table 13: Percentage of patient responses to each question option of the decision aid feasibility questionnaire

Question	Answer options (pt value)	%
1. Did this educational material help you recognize that a decision needs to be made?		
	Not at all (-1)	0
	A Little (-1)	0
	Somewhat (0)	0
	Quite a bit (1)	25

	A great deal (1)	75
	Overall score	1/1
2. Did this educational material prepare you to make a better decision?		
	Not at all (-1)	0
	A Little (-1)	0
	Somewhat (0)	0
	Quite a bit (1)	25
	A great deal (1)	75
	Overall score	1/1
3. Did this educational material help you think about the pros and cons of each option?		
	Not at all (-1)	0
	A Little (-1)	0
	Somewhat (0)	0
	Quite a bit (1)	25
	A great deal (1)	75
	Overall score	1/1
4. Did this educational material help you think about which pros and cons are most important to you?		
	Not at all (-1)	0
	A Little (-1)	0
	Somewhat (0)	0
	Quite a bit (1)	25
	A great deal (1)	75
	Overall score	1/1

5. Did this educational material Help you know that the decision depends on what matters most to you?		
	Not at all (-1)	0
	A Little (-1)	0
	Somewhat (0)	0
	Quite a bit (1)	75
	A great deal (1)	25
	Overall score	1/1
6. Did this educational material help you organize your own thoughts about the decision?		
	Not at all (-1)	0
	A Little (-1)	0
	Somewhat (0)	0
	Quite a bit (1)	0
	A great deal (1)	100
	Overall score	1/1
7. Did this educational material help you think about how involved you want to be in this decision?		
	Not at all (-1)	0
	A Little (-1)	0
	Somewhat (0)	25
	Quite a bit (1)	25
	A great deal (1)	50
	Overall score	0.75/1
8. Did this educational material help you identify questions you want to ask your doctor?		
	Not at all (-1)	0

	A Little (-1)	0
	Somewhat (0)	25
	Quite a bit (1)	0
	A great deal (1)	75
	Overall score	0.75/1
9. Did this educational material prepare you to talk to your doctor about what matters most to you?		
	Not at all (-1)	0
	A Little (-1)	0
	Somewhat (0)	0
	Quite a bit (1)	25
	A great deal (1)	75
	Overall score	1/1
10. Did this educational material prepare you to share the decision making with your doctor?		
	Not at all (-1)	0
	A Little (-1)	0
	Somewhat (0)	0
	Quite a bit (1)	0
	A great deal (1)	100
	Overall score	1/1
	Total	9.25/100

Table 14: Evaluation of objectivity of decision aid based on proportion of patient responses

I found the information in the website	Patient responses (%)
Slanted towards choosing chemotherapy (versus best supportive care alone)	0
Slanted towards choosing FOLFIRINOX (versus gemcitabine)	0
Objective and balanced when presenting the different treatment options	100

Patients were also given the option to describe, in their own words, what they liked and disliked about the decision aid questionnaire within the patient acceptability questionnaire (Table 15). All patients added comments to the question that asked what they liked most about the patient decision. When asked if patients had suggestions to improve the decision one patient left the question blank.

Table 15: Patient written comments to open-ended questions of the acceptability questionnaire

Patient	What did you like about this decision aid?	What suggestions do you have to improve the decision aid?
1	I have a little more courage. I would be more comfortable asking my doctor questions.	Nothing I can think of I can think of.
2	I liked that it was straightforward and that it gave me all the facts.	No
3	It was useful in assigning numeric values to the various options. I wish something like this had been available when I was treated for prostate cancer as did my wife when she was treated for colon cancer.	I am not sure I can make useful suggestions here since, based on my wife's recent experience with chemo we were already familiar with the options.
4	I was interested in everything presented in this decision aid. It opened my eyes to what my options were. Gave me a better understanding of what I need and what I want.	---

5.4. Discussion

In this phase of the project, a decision aid, which was developed for patients with advanced pancreatic cancer considering chemotherapy, was piloted in a small, prospective observational study. The main objective of this pilot was to evaluate the acceptability of a decision aid. It was found that the majority of patients and medical oncologists that participated in the study felt that there was a need for the decision aid, that it was informative and clear, and overall acceptable and feasible.

Four physicians who treated the pancreatic cancer population and were not involved in the design or development of the decision aid responded to the practitioners need assessment questionnaire. Physicians were more or less equally distributed across baseline characteristics in terms of age, and years of practice although there were more females than males. Half the physicians felt that they shared the decision with patients while the other half present the options and advice to the patient, for them to make the decision on their own. The majority of physicians recommended the distribution of an Internet-based decision aid distributed on the same day of consultation as being the optimal delivery format and time. This recommendation was therefore followed for the distribution of the decision aid in the pilot study. All physicians confirmed a need for a decision aid for this population of patients.

Based on findings from the patient needs assessment, decisional needs were greatest in terms of lack of knowledge, lack of support and decisional conflict. These findings suggest that the majority of patients lack the knowledge required to make informed decisions, that they are unsure and not ready to make any decisions and that they do not have sufficient support from others to make the decision. As the average baseline knowledge score for patients included in this study was 64%, which falls between the 50-80% acceptability interval, it could be concluded that the knowledge test itself was acceptable and could be used to test patient knowledge in a larger study. It is hypothesized that the distribution of a decision aid could improve patient knowledge scores. Evidence suggests that the use of oncology decision aids has improved patient knowledge by a mean difference of 13.7% (CI 9.0-18.5%)[88-90,109-113]. Most patients responded correctly to questions related to general information on their disease but were not aware of their treatment options and the details associated with each option. For instance, patients did not know that radiation therapy was not an option for treatment, and that there were more than one treatment option to choose from. Furthermore, they did not know

the differences between the two chemotherapy options, and were unable to answer questions related to the side effects associated with the treatments. This information is all included in the decision aid, which was designed and distributed to patients, thus it can be hypothesized that it would help improve patient knowledge and understanding of their disease and treatment options. Interestingly, all patients demonstrated realistic expectations. The high rate of correct answers for this particular question could be associated with information that patients have gathered from outer resources or from other doctors (family doctor or surgeon). Most incoming patients with advanced pancreatic cancer are required to first have a biopsy and some see a surgeon close to the time that they see their medical oncologist, thus most information about the extent of their disease in terms of it being incurable and non-resectable have already been shared with the patient. It would be of interest to further explore their expectations in depth to determine what they know about survival rates that are associated with each treatment. The findings from the patient needs assessment suggested that there was also a need for a decision aid.

With regards to the social aspects of the decision, it was found in this study that the majority of patients felt that they were choosing without pressure from others such as their doctor, family or friends. Patients were relatively clear about the perceptions of others including their doctors in terms of opinions and practices.

Disease outcomes, prognosis and treatment options are discussed with patients by their oncologist during the first consultation. However, the patients' understanding and retention of information about their diagnoses and about the risks and benefits of the available treatments is unclear. Findings from studies suggest that patients retain little information from what they are told during their consultation and from what is provided in the letter of informed consent[42, 43]. As randomized trials have suggested a role for patient decision aids in oncology to improve patient knowledge and information retention[45-48], it would be of interest to measure patient information retention in the pancreatic cancer patient population.

In terms of what was most important to patients, survival and cancer control were the most important with the highest mean scores and the largest proportion of patients responding that these components were "very important." This was expected, although it was interesting that a small proportion of the

responders also were unsure about this answer. This could reflect the group of patients who feel that avoiding side effects is more important than survival and cancer control. Avoiding side effects was the second most important decisional component with a relatively high mean score and over half the population responding “very important.” Symptom management was also found to be important amongst the majority of patients, which was also expected. However, there appeared to be more uncertainty around quality of life, where the majority of patients were unsure. This could be explained by a lack of understanding of the definition of quality of life, or it being confounded with patients’ perceptions on other related outcomes such as avoiding side effects or symptom management.

When considering survival alone for chemotherapy versus best supportive care, half the patients selected “maybe” while the other half was divided equally between “definitely yes” and “unsure”. This finding was interesting, as it was expected that, based on survival alone, more patients would have been leaning more towards chemotherapy. However, it appeared that patients were unsure about this option based on what they read about survival and were perhaps also unsure whether it is worth having treatment based on only a small improvement in overall survival. When patients were introduced to probabilities around cancer control, however, half the study population answered “definitely yes” which could possibly be associated with the more promising statistics that are associated with cancer control rates in patients treated with chemotherapy. Therefore, although survival rates are low, patients learn that there is a possibility to keep the cancer from growing and consequently, manage their symptoms. The other half of patients that had answered unsure about this consideration, could possibly have not understood the rates, or were still debating whether the statistics of cancer control were worth the pursuit of treatment. Although one half of the patients were unsure about whether they would lean towards chemotherapy or not, when presented with the information on side effects, the other half selected “maybe leaning towards chemotherapy”. There were no responses for “definitely no chemotherapy,” despite its association with side effects, suggesting perhaps that side effects may not be as important for patients who answered survival and cancer control as being most important to them, and therefore the answers balance out. Another possibility is that patients come to the clinic with an initial fear of chemotherapy based on what they may have read or heard or even seen from other patients’ experiences. Once the patients have read the statistics about the chemotherapy, and discussed the rates with their doctor, they may gain a

better idea of what to expect. Consequently, patients are able to decide amongst the different side effects that are associated with the treatments, which one patients would rather avoid over another. Patients can also compare the side effects between the two types of chemotherapy treatment and can quickly see from the 100-faces diagrams that gemcitabine is associated with much less toxicity than FOLFIRINOX. Based on the patient answers for quality of life and symptom management, it appears that more uncertainty falls around these two components. Patients often believe that chemotherapy is more likely to decrease quality of life, based on the side effects that it is associated with. However, most clinical trials have shown that quality of life actually decreases at a slower rate when treated with chemotherapy[28]. This information may confuse patients or surprise them, as they may expect the opposite resulting in more uncertainty about what they would do for this particular consideration. It would be important to clearly define quality of life to the population of patients and highlight its differences with the other outcomes, so that a patient can gather a clearer understanding. Symptom control is another component of the decision that can be complex, as symptoms are caused by the cancer itself, and can vary for every patient. Chemotherapy has been shown to treat cancer related symptoms such as pain, although it can also worsen symptoms such as fatigue, making it more difficult to weigh the two options against each other. Thus, this decision would be significantly based on a patient's preference towards which side effects they would rather avoid. Finally, convenience is a component that can significantly affect a patient's decision, especially for younger patients who are still working, or for the population of patients that depend on others to take them to treatments, or for elderly patients who live alone and require others to take care of them. As expected, these answers were more spread out, where one patient, who considered convenience to be very important, selected "definitely no chemotherapy," while another patient who rated convenience as being "unimportant, selected "definitely yes chemotherapy."

For the decision aid between two the types of chemotherapy FOLFIRINOX, and the single-agent, gemcitabine, the majority of patients were leaning more towards FOLFIRINOX. Although patients had been more uncertain about whether they were leaning towards any chemotherapy or no chemotherapy, where answers were more or less distributed evenly between all options, the majority of the patients (75%) had selected FOLFIRINOX as their treatment choice if they were to pursue treatment. It had been expected that the distribution of responses from the first step of the decision

aid would be reflected in the responses of the second step of the decision aid, where the same proportion of patients that were unsure about chemotherapy in the first step would also either be unsure about FOLFIRINOX in the second step and lean more towards gemcitabine. In contrast, it was surprising that the majority of patients were leaning more towards FOLFIRINOX. This could be explained by the patients' reactions to the new information presented to them about FOLFIRINOX in the decision aid information sheet, which shows the difference in survival and cancer control outcomes between the two forms of treatment. It may also be explained, as stated by a patient in one of their responses, that if a patient is going to pursue a treatment at all, they would rather select the treatment that offers the better survival advantages: "*If I'm going to take chemotherapy, I minus well go all the way."* For side effects, it was interesting that half of the patients were still leaning towards "definitely FOLFIRINOX," despite its association with higher risk of toxicity. Once again, these responses probably reflect patient preferences and values, where survival and cancer control were selected as being most important to them. In terms of quality of life, and in contrast to findings for the quality of life component in the first step of the decision, it was observed that there was less uncertainty with regards to quality of life in the FOLFIRINOX decision aid, measured by the smaller proportion of patients answering "unsure." This may reflect a better understanding of the differences in quality of life between the two treatments, after reading more about it, and better understanding the differences in quality of life between the treatment options[28]. Another possibility for this difference is that the information about quality of life for the FOLFIRINOX decision aid had provided statistics, 100-faces diagrams and was expressed in words, while the chemotherapy decision aid only used words. This suggests that the diagrams and statistics help patients better understand the advantages and disadvantages associated with each treatment. This hypothesis is supported by the literature where it has been shown that many aspects of text presentation can affect comprehension and a patient's ability to use the decision aid[89, 90,113,114].

Overall, patients tended to lean more towards FOLFIRINOX for each of the decisional components in comparison to their decision towards chemotherapy in general. There was a 10% difference in mean scores for overall decisions between the different options. The propensity for FOLFIRINOX for each of the decisional components could be explained by the remarkable difference in overall survival and

cancer control rates between FOLFIRINOX and gemcitabine, which were presented in the information aid, and could be influencing the patients' answers for the other components as well.

To evaluate the overall acceptability and feasibility of the decision aid, patients were asked to complete two ten-item questionnaires adapted from the Ottawa Decision Support Framework questionnaire for acceptability and feasibility. Based on the findings of this pilot study, the decision aid was deemed to be acceptable, as the majority of patients (>90%) had responded that the decision aid was acceptable over all and for each of the questions included in the acceptability questionnaire. In terms of decision aid usability, all patients preferred the use of the Internet as a decision aid, although some patients required assistance by either a family member or member of the health care staff. However, this feedback was promising, as it had been unsure whether an Internet-based decision aid would be well-received by the patient population. Evidence further confirms that interactive web-based formats are effective and improve patient knowledge and decrease decisional conflict[107-108].

Based on the ODSF, decision aids should include information about the problem, alternatives, and benefits and risks in order to improve knowledge and quality of the decision[39]. Results from this pilot study showed that all patients believed the amount of information to be "just right" and that the quality was between very good and excellent for all the different information sections in the decision aid. This decision aid could be considered a more detailed decision aid, based on the definition provided in a meta-analysis conducted by Stacey *et al* and found that the more detailed decision aids were, the greater the improvement in mean knowledge scores over usual care, although differences may be small (Stacey et al 2011)[98]. Information was presented in a balanced manner where both the positive and negative features of each option were clearly stated as per requirements of the IPDAS criteria[94]. Efforts were made to present the available options and the positive and negative information about each of the options in a complete and neutral manner without influencing individuals towards favouring or rejecting any particular option[94]. It was also ensured that information was presented using equal detail in terms of font size, order of reporting, and display of statistics. With regards to the presentation of probabilities, referring to the IPDAS chapter on presentation of probabilities, suitable formats included the use of visual aids such as bar charts, human figure representations, 100-face diagrams and flow diagrams[94]. All patients (100%) had answered that the information in the website was objective and balanced when presenting the different treatment options and not slanted towards

one option or the other. Patients also commented in open-ended answers to the questions that the information presented was objective and presented the facts in a straight forward manner. This is especially important for patients, as the omission of information, especially negative information related to treatment options, the unbalance in diagrams and presentation of numbers with different denominators or presentation of probabilities in different ways can cause the decision aid to be slanted towards one treatment over another and may influence a patient's treatment choice. Recommendations exist, which were followed in this study, to prevent the decision aid from being unbalanced[98,115].

The qualitative component of the decision aid's evaluation was helpful in providing patient narratives of what they liked or disliked about the decision aid. Patient responses were useful where one patient expressed that he wished a decision aid would have been available when he was treated for prostate cancer as his wife did for colon cancer, while a couple of patients mentioned that they liked the straightforward facts and that numeric values had been assigned to each option. This confirms both the need for a decision aid and the patients' desire to know the information and participate in the decision-making process. Additionally, patients felt that the decision aid gave them confidence to ask their doctor questions at the next visit. This information provides further support to the conclusion that the decision aid was acceptable and feasible.

5.4.1. Limitations

Some limitations to this pilot are related to the small sample size of the study. Due to the low incidence rate of pancreatic cancer and the small timeframe available to actively recruit patients, only four patients were included, although six patients had consented. The remaining two patients had not completed all of the questionnaires at the time of the data analysis. For the purpose of the acceptability and feasibility study, however, this sample was sufficient to determine whether the next step of the study was worth pursuing or whether the decision aid should be re-designed or modified to better suit the population of interest. With regards to the population of interest, one possible drawback for this pilot was that median age for the study population (85) was significantly older than the median age of the disease (65). Therefore, it was unclear whether the decision aid would be useful for this population. However, all patients were able to navigate through the decision aid, answer the questionnaires and deemed the decision aid both acceptable and feasible. Because this study

population was elderly, it can also be inferred that the younger population may find the decision aid even more useful. Furthermore, studies have confirmed that elderly patients desire to know information about their options just as much as patients of younger age groups and should be involved in the decision as they understand information presented to them and are able to process it[102-106].

Another limitation includes the fact that the impact the decision aid may have had on patient anxiety, distress and psychosocial functioning was not measured in this study. However, literature suggests that overall, decision aids do not have adverse effects on anxiety, health status or patient satisfaction[116]. Nonetheless, for the purpose of a randomized study evaluating this decision aid, patient anxiety and psychosocial distress would be measured before and after the distribution of the decision aid.

Another limitation was that there is no official threshold value to determine the acceptability or feasibility of a decision aid exists. However, as described in the "Workbook on Developing and Evaluating Patient Decision Aids," a pre-established criteria for success is recommended to use in order to determine its overall acceptability and feasibility in pilot studies, where authors provided an example of 70%[117-119]. The threshold for the purpose of this study was set higher, at 85% based on agreement within the decision aid steering group.

Finally, a final limitation that was considered was that the results of this decision aid could be biased by social desirability bias, where patients provide answers that they think is what the interviewer/doctor/reviewer would approve or want to hear[120-122]. This bias is especially problematic for questions about decision aid acceptability or feasibility. To address this bias, as it had been predicted prior to the design of the decision aid, disclaimers accompanied each questionnaire provided on the website stating that there are no wrong or right answers. Also, patients were given the freedom and privacy to complete these questionnaires at home alone or in the waiting room alone, with the IPAD tablet, in the absence of the doctor, or interviewer, and thus any external pressure. Thus, it can be concluded that this bias was effectively minimized for the purpose of this pilot study.

5.4.2. Conclusion

In conclusion, this pilot indicated that there was a need for a decision aid for patients with advanced pancreatic cancer considering chemotherapy. A small group of selected metastatic pancreatic cancer patients found that this decision aid was acceptable, feasible, as well as potentially useful in making a

treatment decision. All patients indicated that the information provided in the decision aid was objective and well-balanced and the amount of information was just right. All of the patients would recommend this decision aid to others in their situation, and both practitioners and patients selected the use of the Internet as the optimal format of delivery. With the objective of clarifying any misunderstandings about prognosis or treatment choices amongst patients, a decision aid may help decrease decisional conflict and allow patients to be actively involved in the decision making process. If patients are aware of their personal values and preferences, they can communicate this information to their physician and participate in the decision of a treatment option that best suits their needs. The use of a decision aid can also improve physician-patient communication and assist patients with pancreatic cancer in choosing between best supportive care alone, as well as the different chemotherapy options. A decision aid will further assist physicians in understanding their patients' individual preferences and expectations, as physicians play an important role in the decision-making process. By using an online decision aid, continuous updates can be made to the content and decision aid itself, easily accessible by physicians and practitioners from across the country. Furthermore, the online decision aid could also be used as a research tool, where questionnaires can be developed and used to learn more about the study population and to make improvements to the decision aid website. For example, a questionnaire could be added to the website that asks patients about important outcomes in order to use this information for the future design of clinical trials and to provide relevant information and data to the patients.

Based on the favourable findings of the first part of this pilot study, which aimed to evaluate the acceptability and feasibility of the decision aid amongst both patients and physicians, the next step can now be executed which involves the design of a larger scale, prospective randomized trial that evaluates the use of a decision aid on patient outcomes such as knowledge and decisional conflict.

6. GENERAL DISCUSSION AND RECOMMENDATIONS

6.1. Discussion

Pancreatic cancer is a terrible diagnosis that comes with little hope for cure and great need for further research. Since the introduction of gemcitabine as standard therapy in 1997, progress in treatment has been slow. However, the past couple years have been promising with the introduction of a four-drug combination treatment, FOLFIRINOX, and more recently, a gemcitabine-based doublet therapy combined with NAB-Paclitaxel. With the introduction of these treatments amongst several other therapies, there is requirement of a valid comparison of the treatments. Randomized clinical trials between the various treatments would be required in order to determine superiority, however, with the large number of treatments for advanced pancreatic cancer available, the cost of running a trial, and the length of time it would take to reach an answer, this may not be the best solution. Attempts have been made to compare the outcomes between different treatments based on their results from randomized trials compared to a common therapy, such as gemcitabine, although this is considered "breaking randomization" as described by Jansen et al[123]. With the lack of direct evidence and the need to compare multiple therapies, one must rely on indirect evidence to obtain the immediate answers about optimal therapy and accurate effect estimates for the different comparisons that they desire. In order to satisfy this first objective, a systematic review and evaluation of the literature was conducted in order to be as comprehensive and inclusive as possible. After identifying eligible trials, a Bayesian network meta-analysis was performed to obtain the effect estimates for all comparisons and identify the treatment associated with greatest survival and safety outcomes. Our network meta-analysis found FOLFIRINOX to be ranked first amongst all other treatments and associated with the greatest effect estimates for overall survival with statistically significant credible intervals. However, we also found that FOLFIRINOX was associated with increased odds for grade 3 or 4 adverse events. In contrast, gemcitabine offered modest survival outcomes with lower risk for developing side effects. Identified as two suitable treatments that are situated at opposite ends of the spectrum, in terms of survival and safety outcomes, the need to consider both the benefits and risks of each treatment is important when deciding on which treatment a patient should pursue. As the decision between treatments was found to be preference-sensitive, it was of interest to develop a decision aid to assist patients in the decision

making process. The design of the decision aid involved following the appropriate steps of the development process in order to present high quality and current information to patients in a comprehensible and transparent manner. By carefully following guidelines implemented by the Ottawa Decision Aid Research Group, a patient decision aid for patients with pancreatic cancer considering chemotherapy was created to take patients through two important steps of the decision process: the decision between chemotherapy or no chemotherapy, and if leaning towards chemotherapy, the decision between FOLFIRINOX and gemcitabine. These two treatments were selected as the main options, as gemcitabine is the standard treatment that is associated with less toxicity, while FOLFIRINOX is the more aggressive option. It is possible that other therapies will be introduced to patients in the future, such as gemcitabine plus NAB-paclitaxel, however at present, this is not a drug funded in Ontario and more research must be done to confirm whether it should be presented as a standard. In the final phase of the study, a pilot study was conducted to evaluate the overall acceptability and feasibility of the decision aid. A small sample was selected to read the information provided on the website and to work through the decision tool where they were then asked to rate it through a series of questionnaires that have been validated in previous studies. Overall, patients and physicians perceived the decision aid as both useful and acceptable. Navigation through the different links of the website was found to be intuitive and straightforward and the content presented to patients was appropriate. General improvement in patient knowledge scores was observed, while patients felt confident about their decision after the use of the decision aid. One remarkable thing was that patients felt the decision aid allowed them to prepare for their consultation and think of questions to ask their medical oncologist that they wouldn't have otherwise asked. Patients commented that it allowed them to know what their options were and felt comfortable asking questions about their options afterwards. Based on the physician questionnaire post-consultation, they also felt that patients asked more questions and were more involved in the decision making process during their visit. All patients would recommend the use of the decision aid to others in their same situation to help them through the decision-making process.

In summary, this study involved the identification of a need to better inform and guide patients with newly diagnosed advanced pancreatic cancer though their treatment decisions. Beginning with a systematic search of the literature, important clinical trials were identified where treatments were

indirectly compared to each other through a network meta-analysis and findings were used for the development and implementation of the intervention: a patient decision aid. This decision aid is helpful to both patients and physicians and can help bridge the gap in knowledge between research and clinical practice.

6.2. Recommendations and next steps

6.2.1. Future consideration for network meta-analysis

The use of network meta-analysis can be very informative and important in guiding physicians and researchers to the development of more beneficial treatments for advanced pancreatic cancer. It may also help direct the design of future clinical trials and where research dollars should be spent. There is still a far way to go in the advancement of treatment for metastatic pancreatic cancer, and as drugs such as FOLFIRINOX and gemcitabine plus NAB-Paclitaxel may bring research two steps closer and the development of future drugs, the pursuit for an optimal treatment that is tolerable and safe that significantly improves survival outcomes continues. As new drugs and combination therapies are developed for advanced pancreatic cancer, periodical updates to the network meta-analysis will be important in order to continue to direct research. By indirectly comparing new treatments as they are introduced, researchers and physicians can get a quick and general idea of whether the treatment is worth further pursuing as a prospective standard therapy or comparator in future clinical trials. For instance, our network meta-analysis identified FOLFIRINOX and gemcitabine plus NAB-Paclitaxel as being two possible options for use as a standard treatment. Being associated with different benefits and risks, the question arises whether the two should be compared with each other in a head to head trial. While a network meta-analysis can relay important information about the general efficacy and tolerability of treatments in a timely manner with no associated costs, the cost of conducting multi-center trials in order to compare all of the treatments found to have a statistically significant survival benefit would be very high and results may not be conclusive. For instance, in order to prove a significant difference in survival for FOLFIRINOX over gemcitabine + nab-Paclitaxel in a randomized clinical trial at 80% power and 0.05 level of significance, approximately 678 patients would need to be recruited. At an accrual rate of 226.2, this would take 3 years to achieve with 1.5 years of follow up. Although a formal economic evaluation to look at uncertainty and cost minimization study would need

to be performed to confirm the impact, this trial could cost around 40 million dollars if the cost of treatment and running the trial is taken into consideration. Thus, results from a periodically updated network meta-analysis can guide physicians in the recommendations of different treatments while awaiting results from ongoing clinical trials.

6.2.2. Future directions for the patient decision aid

6.2.2.1. Modification and addition of decision arms

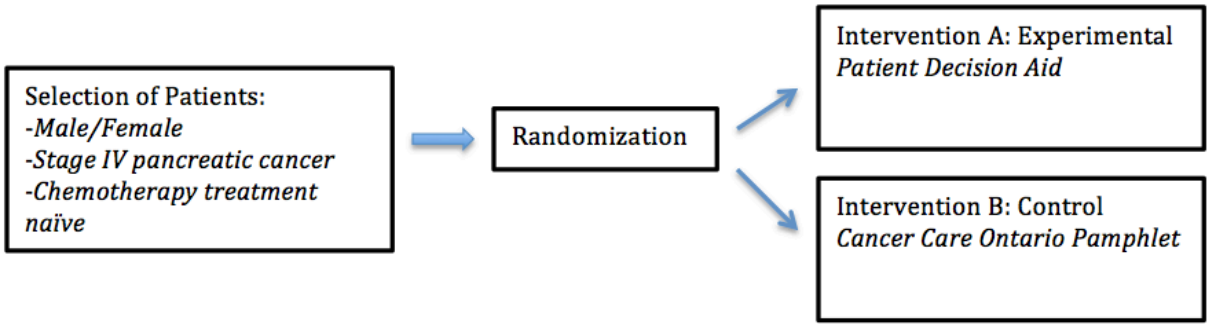
As the network meta-analysis continues to be updated with incoming trials, it is possible that new therapies will be introduced as standard treatment for this population and will have to be included as additional arms to the decision aid. Due to the two-step design of the decision aid, and an Internet-based format, the addition of new treatment decision arms will not be difficult or confusing for patients to comprehend. Within the next year, and depending on final results from the gemcitabine and NAB-Paclitaxel study, it is possible that information on this treatment, the benefits and side effects associated with the treatment and its outcome rates will be added to the decision aid. Continuous modification of the decision arms are expected as shifts in survival and safety as well as treatment development will drive cancer research forward and lead to more innovative and effective therapies to hopefully better treat advanced pancreatic cancer.

6.2.2.2. Randomized clinical trial of the decision aid

Our decision aid was well received by both patients and physicians resulting in the introduction of several new ideas for further development of the decision aid and its implementation. First of all, in order to determine whether the application of the decision aid is superior to other information guides and standard patient care, it would be of interest to design and conduct a larger-scale randomized clinical trial. A multi-center, single blinded trial, where physicians are blinded to the intervention patients receive, could further determine the impact of a decision aid on outcomes such as patient knowledge and expectations, decisional conflict and even survival outcomes. Patients in the

experimental arm would be randomized to receive the decision aid, while patients from the control arm could receive the standard Cancer Care Ontario pamphlet that is readily available to patients in the clinic. Upon completion of the trial, it would be of interest to submit the final decision aid to the Ottawa Hospital Decision Aid online directory as well as make the pamphlet version of the decision aid available across all Canadian cancer centers. Knowledge Translation strategies would need to be developed that that further makes the decision aid available to all patients, physicians and health-care practitioners in Canada.

Figure 31: Randomization chart of a proposed clinical trial design to compare the patient decision aid to standard care



6.2.2.3. Cost-effectiveness of the decision aid

The idea of introducing the decision aid to pancreatic cancer patients prior to their surgical consultation was suggested as a way to reduce costs and risk of surgical complication associated with biopsy of the pancreatic tumour. For example, at the Ottawa Hospital Cancer center, patients are required to have a biopsy of their tumour prior to their consultation with the medical oncologist in order to determine the pathology and histologic grade of the tumour. Therefore, all patients deemed unresectable by the hepatobiliary surgeon must first undergo fine needle biopsy and histological confirmation of the disease before their appointment is even made with a medical oncologist. There is a waiting time associated with the procedure itself, as well as a wait time associated with processing and receipt of biopsy results and finally, with the appointment being made to see the medical oncologist. Some patients may wait over a month after their diagnosis before they see the medical oncologist. The chemotherapy decision aid delivered to patients prior to their biopsy and appointment

with the medical oncologist may prevent unnecessary biopsies for patients who are leaning towards not having chemotherapy and consequently prevent the patients from undergoing a surgical procedure, which is still invasive to a certain extent and may be associated with surgical complications such as infection. Patients could also avoid additional anxiety or stress from the procedure itself and from waiting for their upcoming appointment with the medical oncologist. On the other hand, patients who are leaning towards chemotherapy would be able to potentially move up on the waiting list and see the medical oncologist earlier and consequently start treatment earlier as well and avoid additional psychosocial stress.

A cost-effective analysis is of particular interest for this particular situation, as the economic burden of advanced pancreatic cancer is quite high, despite its low incidence rate. The mean total cost of direct medical costs associated with pancreatic cancer are $65,500, based on the review from O'Neill *et al*[124]. It was found that hospitalizations from side effects and cancer-directed procedures accounted for the majority of the health care costs. This being said, it is hypothesized that the prevention of side effects from chemotherapy in patients who may not wish to pursue it in the beginning as well as minimization of costs associated with the biopsy procedure, would significantly decrease the cost impact of the disease.

6.3. Closing remarks

The principal aim of this thesis was to contribute to the evidence based knowledge surrounding the treatment of advanced pancreatic cancer by first indirectly comparing the various therapies that have been introduced over the past disease in order to determine the optimal therapy as well as alternative less toxic therapies for patients. The first phase of the thesis had strong clinical relevance, as there is much controversial debate around survival and safety issues associated with various treatments, and physicians and researchers have been attempting to compare these rates in a timely and cost-effective manner. Recognizing that there was an important decision that needed to be made for both patients and physicians, which depended on a patient's preferences and the physician's assessment of their overall health and tolerability, it was hoped that a tool could be designed that would translate and disseminate the knowledge in a way that patients would also have access to the information and

understand the benefits and risks associated with their treatment choices in order to make informed choices. The distribution of an Internet-based decision aid was decided to be the most effective way of communicating this information and guiding patients through the various steps of their decision in order for patients to be able to share the decision making process with their oncologists. With a large research base in patient decision aids, especially within the Ottawa Decision Aid Research Group, a decision aid was designed based on the well-studied Ottawa Decision Framework as well as the components of IPDAS. As no decision tool has ever been designed for this particular population of patients, and it was unclear whether an online decision aid would be feasible and accepted by patients, a pilot of the decision aid was first tested amongst a small sample of the patient population in a prospective observational needs assessment study. Results from this study suggested that the decision aid was very feasible and acceptable amongst patients of all ages and backgrounds; thus, the next step will be to pilot the decision in a larger scale randomized study. This project represents important stepping-stones towards the implementation of this decision tool in clinical practice for all pancreatic cancer patients across the country. Therefore, it will be essential to continue to modify and update the network meta-analysis and decision aid to maintain its quality and validity. Finally, the use of the decision aid in the clinic should be ongoing where future patients can continue to rely on the information presented and decision guide to assist them in making important decisions about their health care. As decision aids become more popular in the oncology setting, it is hoped that this decision aid can be further developed to guide patients with all stages of pancreatic cancer through the various treatment decisions that they face.

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APPENDIX 1: SEARCH STRATEGY FOR OVERVIEW OF SYSTEMATIC REVIEWS

1. Summary of the terms used alone or in combination for acquisition of evidence

Primary MeSH terms	Intervention	Comparator	Outcomes
Pancreas	Drug-therapy	Nucleoside analog	Survival rate
Pancreatic duct (s)	Monoclonal antibodies	Deoxycitidine	Prognosis
Metastatic disease	Combined chemotherapy	2,2 difluoro-deoxycitidine	Survivorship
Adenocarcinoma	Antineoplastics	Single-agent Gemcitabine	Treatment outcomes
Advanced pancreatic cancer	First-line chemotherapy	Gemcitabine	Clinical efficacy
Neoplasm metastasis	Therapeutic treatment	Gemzal	Median survival
Clinical trial(s)	Clinical trials, Phase III	Deoxynucleoside	Time to Progression/Progression Free Survival

2. Search strategy

Database: Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>

---

1 (((advanced or metastatic) and pancreatic cancer) or adenocarcinoma or pancreas* or malign* neoplasm).ti,ab,sh. (6800)
2 (gemcitabine/ and pancreas/) or pancreatic cancer/ or pancreatic neoplasms).ti. (570)
3 limit 2 to yr="1997-Current" (396)
4 limit 3 to clinical trial, phase iii (83)

Search for abstracts in major scientific meeting databases: American Society of Clinical Oncology (ASCO) Library of Abstracts:

Database: ASCO annual meeting, ASCO gastrointestinal meeting

---

1 advanced OR metastatic AND pancreatic cancer OR adenocarcinoma OR AND chemotherapy OR gemcitabine (1217)
2 limit 1 to yr= "2010-current" (419)
3 limit 2 to clinical trial, phase iii (65)

APPENDIX 2: RESULTS OF THE SIGN 50 METHODOLOGY CHECKLIST 2: CONTROLLED TRIALS

SIGN50 Items

1. The study addresses an appropriate and clearly focused question
2. The assignment of subjects to treatment groups is randomized
3. An adequate concealment method is used
4. Subjects and investigators are kept 'blind' about treatment allocation
5. The treatment and control groups are similar at the start of the trial
6. The only difference between groups is the treatment under investigation
7. All relevant outcomes are measured in a standard valid and reliable way
8. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?
9. All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)
10. Where the study is carried out at more than one site, results are comparable for all sites
11. How well was the study done to minimize bias?
12. Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?
13. Are the results of this study directly applicable to the patient group targeted by this guideline?
14. **Notes.** Summarize the authors' conclusions. Add any comments on your own assessment of the study and the extent to which it answers your question and mention any areas of uncertainty raised above.

Study: Author	Study: Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bramhall	2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10.00%	Yes	can't say	High quality (++)	Yes	Yes	No statistically significant difference.
Louvet	2005	Yes	Yes	Yes	No	Yes	Yes	Yes	can't say	Yes	Yes	Acceptable (+)	Yes	Yes	No statistically significant difference.
Reni	2005	Yes	Yes	Yes	No	Yes	Yes	Yes	8.50%	Yes	Yes	Acceptable (+)	Yes	Yes	Statistically significant difference.
Cunningham	2009	Yes	Yes	Yes	No	Yes	Yes	Yes	11%	Yes	can't say	Acceptable (+)	Yes	Yes	Statistically significant difference.
Kindler	2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	24%	Yes	can't say	High quality (++)	Yes	Yes	No statistically significant difference.
Moore	2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12%	Yes	Yes	High quality (++)	Yes	Yes	Statistically significant difference.
VanCustem	2004	Yes	Yes	Can't say	Yes	Yes	Yes	Yes	10.30%	Yes	Yes	High quality (++)	Yes	Yes	No statistically significant difference. Good safety profile.
Riess	2005	Yes	Yes	Can't say	No	Yes	Yes	Yes	19.40%	Yes	Yes	Acceptable (+)	Yes	Yes	No statistically significant difference.
Berlin	2002	Yes	Yes	Can't say	No	Yes	Yes	Yes	19.40%	Yes	Yes	Acceptable (+)	Yes	Yes	No statistically significant difference.
Abou-Alfa	2006	Yes	Yes	Yes	No	Yes	Yes	No	10%	Yes	can't say	Acceptable (+)	Yes	Yes	No statistically significant difference.
Philip	2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	31.20%	Yes	Yes	High quality (++)	Yes	Yes	No statistically significant difference.
Heinemann	2006	Yes	Yes	Can't say	No	Yes	Yes	Yes	19.40%	Yes	Yes	Acceptable (+)	Yes	Yes	No statistically significant difference.
Goncalves	2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9%	Yes	can't say	High quality (++)	Yes	Yes	No statistically significant difference.
Herrmann	2005	Yes	Yes	Can't say	No	Yes	Yes	Yes	19.40%	Yes	Yes	Acceptable (+)	Yes	Yes	No statistically significant difference.
Viret	2004	Yes	Yes	Can't say	No	Yes	Yes	Yes	19.40%	Yes	Yes	Acceptable (+)	Yes	Yes	No statistically significant difference.
Rocha Lima	2004	Yes	Yes	Can't say	No	Yes	Yes	Yes	19.40%	Yes	Yes	Acceptable (+)	Yes	Yes	No statistically significant difference.
Stathopoulos	2006	Yes	Yes	Yes	Yes	Yes	Yes	No	can't say	Yes	Yes	Acceptable (+)	Yes	Yes	Progression free survival not reported. No hazard ratios reported. Power not reported.
Colucci2010	2010	Yes	Yes	Yes	No	Yes	Yes	Yes	can't say	Yes	Yes	Acceptable (+)	Yes	Yes	No statistically significant difference.
Colucci	2002	Yes	Yes												
Poplin	2006	Yes	Yes	yes	Can't say	No	No	Yes	7%	Yes	Yes	Acceptable (+)	Yes	Yes	No statistically significant difference.
Oettle	2005	Yes	Yes	Yes	No	Yes	Yes	Yes	0	Yes	can't say	Acceptable (+)	Yes	Yes	No statistically significant difference.
VanCustem2009	2009	Yes	Yes	yes	yes	yes	yes	yes	can't say	yes	can't say	High quality (++)	Yes	Yes	No statistically significant difference.
Conroy	2011	Yes	Yes	Yes	No	No	Yes	Yes	can't say	Yes	Yes	Acceptable (+)	Yes	Yes	Some differences between study arms. Statistically significant survival benefit.
Von Hoff	2013	Yes	Yes	Yes	No	Yes	Yes	Yes	can't say	Yes	Yes	Acceptable (+)	Yes	Yes	Statistically significant difference.

APPENDIX 3: NETWORK META-ANALYSIS STEPS USING WINBUGS

3.1 NMA code implementation

WinBUGS (Bayesian inference Using Gibbs Sampling) is a computer software that uses Bayesian inference to fit complex models that include both direct and indirect comparisons. It is an open-source Windows computer software that can be downloaded from: https://www.bris.ac.uk/cobm/research/mpes/mtc.html

3.1.1 Preparing the data for WinBUGS

A specific format exists for data entry in order for the code to properly run. Treatments are numbered consecutively starting at one, where the reference comparator, such as Gemcitabine in this case, must be treatment "1". Depending on the outcome of interest, data can be organized in two different ways. For continuous variables, such as overall survival and progression free survival, where hazard ratios are sought columns include the reference treatment 1, labeled t[1] followed by the comparator treatments t[2] that are numbered consecutively from 2. The last three columns include the log hazard ratio (LHR) associated with the reference comparator, followed by its standard error and the number of arms of the trials, respectively (See example x.1).

Example 3.1:

```
# ns= number of studies; nt=number of treatments
list(ns=23, nt=19)
t[,2]   t[,1]   LHR[,2]  se[,2]   na[]
1       2       -0.562118918  0.12341759    2
1       3       -0.328504067  0.077184362   2
1       4       -0.198450939  0.126295221   2
1       4       -0.127833372  0.092729824   2
1       5       -0.116533816  0.119898885   2
1       5       -0.248461359  0.087485906   2
1       6       -0.223143551  0.154233108   2
1       6       -0.083381609  0.229386811   2
1       6       0.09531018    0.106285308   2
1       7       -0.198450939  0.117434112   2
1       8       0.039220713   0.095399602   2
1       9       -0.020202707  0.092848311   2
1       10      0.039220713   0.111407564   2
1       11      -0.072570693  0.1168645     2
1       11      0.124868982   0.194335577   2
1       12      -0.430782916  0.212734626   2
1       13      -0.198450939  0.092095241   2
1       14      0.013902905   0.130442614   2
1       15      -0.029558802  0.091284964   2
1       16      -0.010050336  0.136939059   2
13      17      -0.116533816  0.094072383   2
1       18      0.2390169     0.213389527   2
1       19      0.058268908   0.076868584   2 END
```

In the case of ordinal outcomes such as adverse events, the first column represents the number of adverse events associate with the comparator treatment (t[1]), followed the number of patients in that arm, the number of adverse events for treatment arm 2 and its associated sample size and finally the last three columns refer to the reference treatment, the comparator and the number of arms (see example x.2).

```
# NT=no. treatments, NS=no. studies;  NP = number of placebo/reference treatment trials
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#        per trial in the dataset. In this dataset M is 2.

list(NS=19, NT=17, NP=19)

r[,1]     n[,1]     r[,2]     n[,2]     t[,1]     t[,2]     na[]
0.5       208       1         305       1         2         2
5         158       7         158       1         5         2
11        70        16        60        1         6         2
14        47        43        52        1         7         2
16        41        24        42        1         4         2
17        236       30        230       1         8         2
26        174       53        175       1         9         2
26        189       46        186       1         3         2
29        52        26        50        1         10        2
30        153       34        155       1         3         2
35        167       75        164       1         11        2
35        273       123       273       1         12        2
43        156       32        157       1         13        2
54        247       87        251       1         4         2
54        169       65        173       1         6         2
102       342       137       331       1         14        2
116       430       164       431       1         15        2
84.845    355       84.113    361       1         16        2
48.79     287       62.16     296       1         17        2
END
```

3.2 NMA code

3.2.1 Code for continuous outcomes

```
# Normal likelihood, Relative Effect Data

# Fixed Effect model. Does not account for correlation in multi-arm trials

model{

        for (i in 1:ns){

                for (k in 2:na[i]){

                        prec[i,k]<- 1/(se[i,k]*se[i,k])                                    #Precision of
differences = 1/var
```

```
                    LHR[i,k]~dnorm(delta[i,k],prec[i,k])        #Likelihood for mean differences between arms
                    delta[i,k]<- d[t[i,k]] - d[t[i,1]]          #Define functional parameters for t[i] vs b[i]
                    dev[i,k]<-(LHR[i,k]-delta[i,k])*(LHR[i,k]-delta[i,k])*prec[i,k]
                }
                sdev[i]<- sum(dev[i,2:na[i]])
        }
        resdev<-sum(sdev[])


d[1]<-0
for (k in 2:nt) {d[k] ~ dnorm(0,.0001) }                    # vague priors for basic parameters

# Ranking and prob treatment k is best
        for (k in 1:nt) {
                rk[k]<- rank(d[],k)
                best[k]<-equals(rk[k],1)
                                second[k]<-equals(rk[k],2)
                                        third[k]<-equals(rk[k],3)
                                                fourth[k]<-equals(rk[k],4)
                                                        }
# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
    HR[c,k] <- exp(d[k] - d[c] }}}
```

3.2.2 Code for adverse event data

Fixed effects model for multi-arm trials (any number of arms) - developed based on WinBUGS code from multi-parameter Evidence Synthesis Research Group at the University of Bristol: Website: www.bris.ac.uk/cobm/research/mpes

```
model{
```

```
for(i in 1:NS){
            delta[i,1]<-0
            mu[i] ~ dnorm(0,.0001)                                  # vague priors for baselines
            for (k in 1:na[i])  {
                r[i,k] ~ dbin(p[i,k],n[i,k])                              # binomial likelihood
        logit(p[i,k])<-mu[i] + delta[i,k]                                                  # model
        r0[i,k]<-r[i,k]+0.01*equals(r[i,k],0) -0.01*equals(r[i,k],n[i,k])
                p0[i,k]<- max(p[i,k],.001)
                r.hat[i,k]<- p0[i,k]*n[i,k]

               #Deviance calculation for binomial data
                dev[i,k]<- 2*(r0[i,k]*log(r0[i,k]/r.hat[i,k]) + (n[i,k] - r0[i,k])*log((n[i,k] - r0[i,k])/(n[i,k] - r.hat[i,k])))

                 }

for (k in 2:na[i]) {

          delta[i,k] <- d[t[i,k]] - d[t[i,1]]
                 }

            sdev[i]<-sum(dev[i,1:na[i]])
 }
resdev<-sum(sdev[])

d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) }              #  vague priors for basic parameters

# Treatment 1 baseline, based on average of NP trials including it.
for (i in 1:NS) { mu1[i] <- mu[i] * equals(t[i,1],1) }
for (k in 1:NT)  { logit(T[k])<- (sum(mu1[])/NP) +d[k] }
# ranking
for (k in 1:NT) { rk[k]<- rank(T[],k)
              best[k]<-equals(rk[k],1)}
# pairwise ORs
```

```
for (c in 1:(NT-1)) {  for (k in (c+1):NT)  { or[c,k] <- exp(d[k] - d[c])

        RR[c,k]<-T[k]/T[c]}  }}
```

3.3 Steps for running code

1. **Checking the model:** 'Model' tool was first opened from menu bar and the option "check model" was selected. WinBuGS then notified the user that "model is syntactically correct' which indicates that user can proceed to next step.
2. **Loading the data:** Data is loaded by highlighting the world "List" form the model and selecting the "Load Data" button, followed by highlighting the first row of the data table (as shown in examples above) and re-clicking "Load Data". WinBugs will indicate that data has been successfully loaded and one can move to the next step.
3. **Compiling the data:** The number of chains must first be entered in the box, which was 3, in this case, and then the user must compile the model by clicking the "compile" button. This allows the data structures to be prepared for the sampling procedure.
4. **Loading inits**: Pre-specified values for each of the three chains and corresponding to the number of studies and treatments included in the analysis must be loaded. This is accomplished by highlighting each chain and loading the inits, and then generating the initial values.
5. **Updating the model:** The update tool is used to run the amount of multiple treatment comparisons to be carried out. In the case of this model, 40,000 updates were performed.
6. **Variables of interest:** After the updates were complete, variables of interest including HR (hazard ratio), best, rk (rank), resdev (residual deviance), totresdev (total residual deviance), dev (deviance criterion), sd (standard deviation), etc. were selected and updates were run again.
7. **Obtaining the data:** Data for each of the selected variables were then obtained for both fixed and random effects models and appropriate comparisons could be carried out to determine the model of choice for the other outcomes of interest.

Detailed descriptions and explanations for all available models provided by Ades AE et al. are included in the following weblink: www.bris.ac.uk/cobm/docs/intro%20to%20mtc.doc

3.4 Fixed effects vs. Random effects model

	Median	LCL	UCL	Median	LCL	UCL	LEGEND	
HR[1,2]	1.754	1.379	2.235	1.76	1.23	2.511	1	Gemcitabine
HR[1,3]	1.389	1.194	1.616	1.388	1.018	1.899	2	FOLFIRINOX
HR[1,4]	1.164	1.005	1.349	1.17	0.9207	1.491	3	Gem+nabp
HR[1,5]	1.225	1.066	1.407	1.216	0.9551	1.539	4	Gem+Oxali
HR[1,6]	1.017	0.8665	1.193	1.03	0.829	1.318	5	Gem+Cape
HR[1,7]	1.22	0.9702	1.535	1.219	0.8573	1.729	6	Gem+Cis
HR[1,8]	0.9608	0.797	1.158	0.9592	0.691	1.33	7	Gem+5FU
HR[1,9]	1.021	0.8497	1.225	1.022	0.7337	1.413	8	Gem+5FU+FA
HR[1,10]	1.014	0.8652	1.188	1.017	0.793	1.298	9	Gem+pemetrexed
HR[1,11]	0.883	0.6042	1.292	0.8788	0.5567	1.397	10	Gem+Irino
HR[1,12]	1.537	1.013	2.339	1.543	0.9473	2.518	11	Gem+exatecan

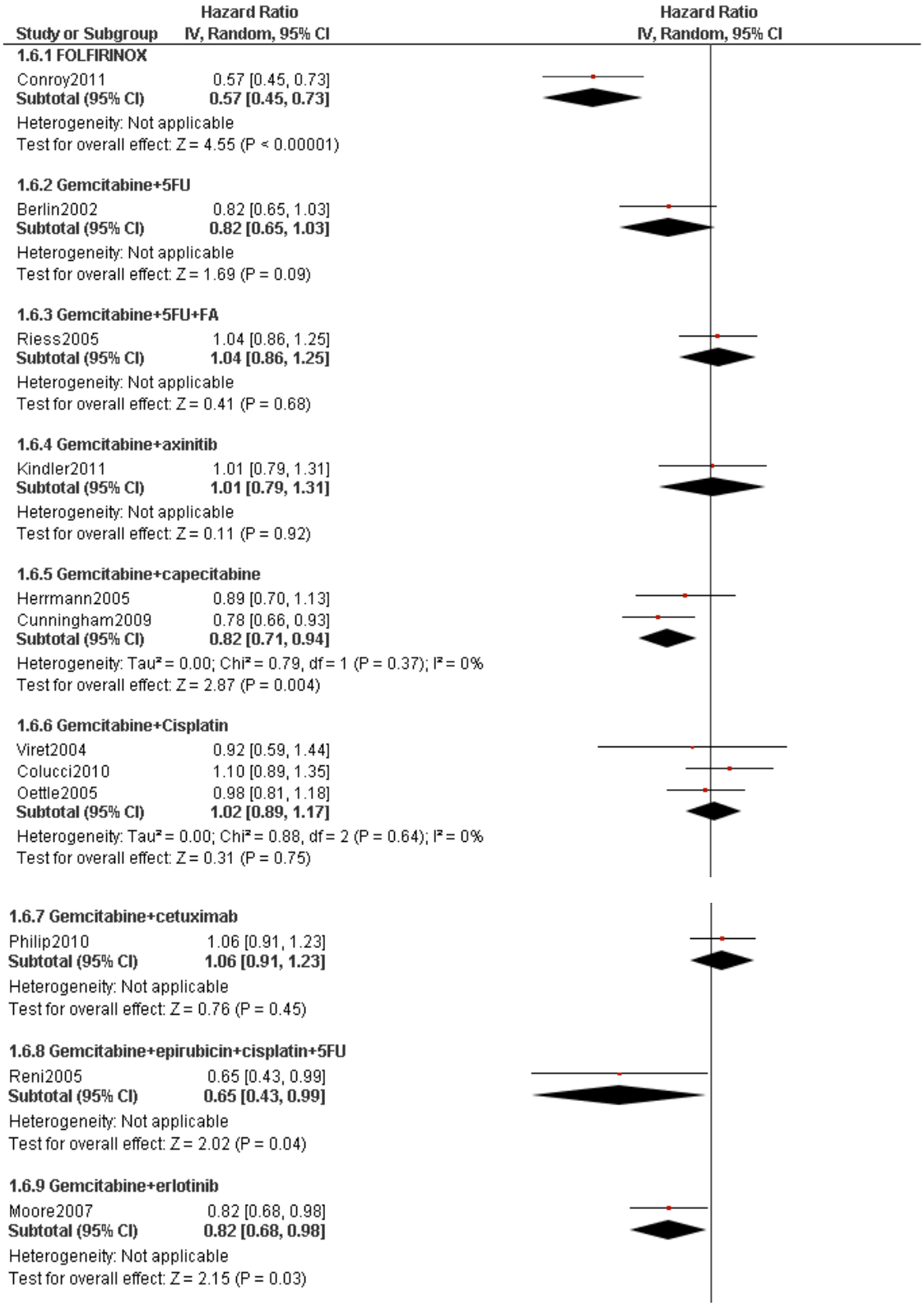
HR[1,13]	1.22	1.018	1.462	1.22	0.8789	1.69	12	Gem+epi/cis/5FU
HR[1,14]	0.9861	0.7635	1.271	0.9881	0.6822	1.426	13	erlotinib
HR[1,15]	1.03	0.8609	1.231	1.03	0.7431	1.425	14	axinitib
HR[1,16]	1.01	0.7733	1.32	1.009	0.6951	1.474	15	tipifarnib
HR[1,17]	1.37	1.059	1.775	1.373	0.8586	2.183	16	marimastat+gem
HR[1,18]	0.7864	0.5177	1.194	0.7816	0.4742	1.282	17	Gem+erlotinib+bev
HR[1,19]	0.9434	0.8107	1.097	0.9447	0.6926	1.283	18	Sorafenib
DIC	-15.121					-13.679	19	cetuximab
resdev	22.45	SE	6	21.94	SE	6.2		

3.5 Summary of included/excluded studies in a priori sensitivity analyses. All experimental treatments in table were compared to gemcitabine alone. **Comparator gemcitabine+erlotinib.**If KPS was reported en lieu of ECOG performance status, the equivalent value (KPS >80%) was used instead.*

Author (year)	Experimental Treatment	**Included in sensitivity analysis (Y/N):**			
		Year of publication >2007	Number of patients/arm >100	Proportion Stage IV >75%	Proportion ECOG 0-1** <85%
Bramhall (2002)	Gemcitabine +Marismastat	N	Y	N	N
Berlin (2002)	Gemcitabine+5FU	N	Y	N	Y
VanCustem (2004)	Gemcitabine +Tipifarnib	N	Y	Y	Y
Rocha Lima (2004)	Gemcitabine+ Irinotecan	N	Y	Y	Y
Louvet (2005)	Gemcitabine +Exatecan	N	N	N	Y
Reni (2005)	Gemcitabine + Oxaliplatin	N	N	N	N
Riess (2005)	Gemcitabine +epirubicin +cisplatin+5FU	N	Y	Y	Y
Oettle (2005)	Gem+	N	Y	Y	N

	Capecitabine				
Abou-Alfa (2006)	Gem+Pemetrexed	N	Y	Y	Y
Heinemann (2006)	Gemcitabine +Cisplatin	N	N	Y	N
Stathopoulos (2006)	Gemcitabine +Irinotecan	N	N	N	N
Poplin (2006)	Gemcitabine + Oxaliplatin	N	Y	Y	Y
Herrmann (2007)	Gemcitabine+5FU +folinic acid	N	Y	Y	Y
Moore (2007)	Gemcitabine +Erlotinib	N	Y	Y	Y
Cunningham (2009)	Gem + Capecitabine	Y	Y	N	Y
VanCustem (2009)	Gem+Erlotinib+ Bevacizumab*	Y	Y	Y	Y
Philip (2010)	Gemcitabine + Cetuximab	Y	Y	Y	Y
Colucci (2010)	Gem+Cisplatin	Y	Y	Y	Y
Kindler (2011)	Gem+Axinitib	Y	Y	N	N
Conroy (2011)	FOLFIRINOX	Y	Y	Y	N
Goncalves (2012)	Gem+Sorafenib	Y	N	N	N
Heinemann (2012)	Capecitabine+ Erlotinib*	Y	Y	Y	Y
Von Hoff (2013)	Gem+ NAB-Paclitaxel	Y	Y	Y	Y

APPENDIX 4: FOREST PLOT OF PAIRWISE COMPARISON FOR NINETEEN TREATMENT COMPARISONS



1.6.10 Gemcitabine+exatecan

Abou-Alfa2007 1.13 [0.77, 1.66]
Oreilley2004 0.93 [0.74, 1.17]
Subtotal (95% CI) 0.98 [0.81, 1.19]
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

1.6.11 Gemcitabine+irinotecan

RochaLima2004 1.04 [0.84, 1.29]
Subtotal (95% CI) 1.04 [0.84, 1.29]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.72)

1.6.12 Gemcitabine+marismastat

Bramhall2002 0.99 [0.76, 1.29]
Subtotal (95% CI) 0.99 [0.76, 1.29]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)

1.6.13 Gemcitabine+nab-Pacletaxel

VonHoff2013 0.72 [0.62, 0.84]
Subtotal (95% CI) 0.72 [0.62, 0.84]
Heterogeneity: Not applicable
Test for overall effect: Z = 4.26 (P < 0.0001)

1.6.14 Gemcitabine+Oxaliplatin

Louvet2005 0.82 [0.64, 1.05]
Poplin2006 0.88 [0.73, 1.06]
Subtotal (95% CI) 0.86 [0.74, 0.99]
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.04 (P = 0.04)

1.6.15 Gemcitabine+pemetrexed

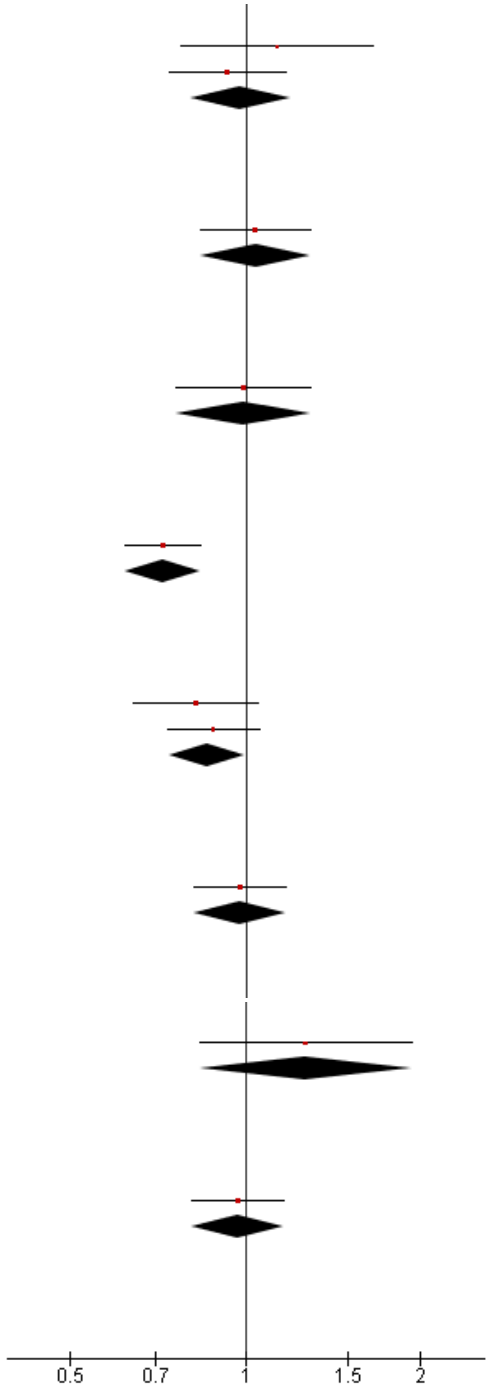
Oettle2005 0.98 [0.82, 1.18]
Subtotal (95% CI) 0.98 [0.82, 1.18]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)

1.6.16 Gemcitabine+sorafenib

Goncalves2012 1.27 [0.84, 1.93]
Subtotal (95% CI) 1.27 [0.84, 1.93]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)

1.6.17 Gemcitabine+tipifarnib

VanCustem2004 0.97 [0.81, 1.16]
Subtotal (95% CI) 0.97 [0.81, 1.16]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)

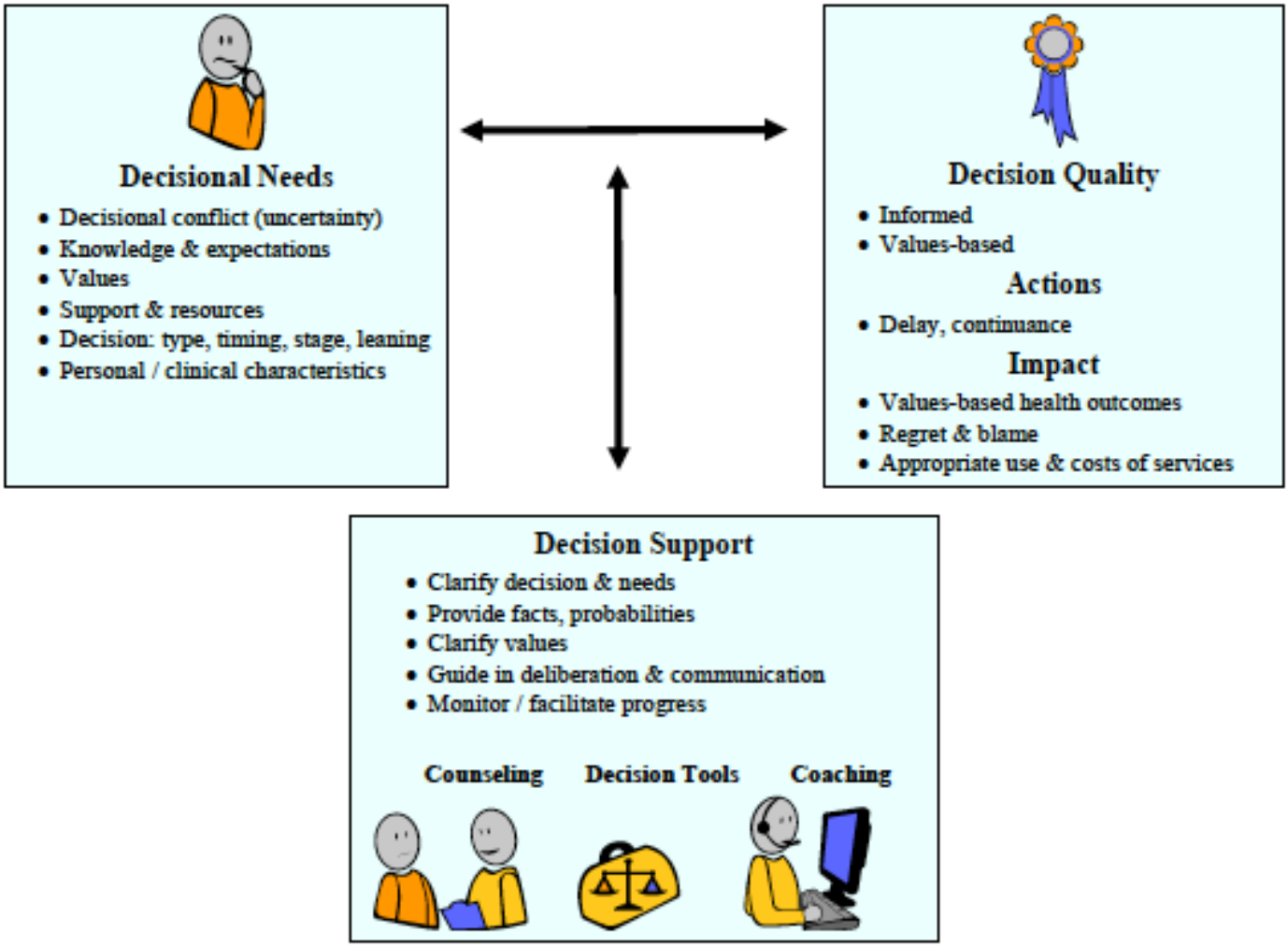


Favours comparator Favours gemcitabine

APPENDIX 5: THE OTTAWA DECISION SUPPORT FRAMEWORK

The Ottawa Decision Support Framework (Fig 1) uses concepts and theories from general psychology (Tversky & Kahneman, 1981), social psychology (Ajzen & Fishbein, 1980), decision analysis (Keeney, 1982), decisional conflict (Janis & Mann, 1977), values (Fischoff, Slovic & Lichtenstein), social support (Norbeck, 1988; Orem, 1995), and self efficacy (Bandura, 1982).

Figure 1. Ottawa Decision Support Framework



The framework applies to all participants involved in decision making, including the individual, couple, or family, and their health practitioner. The framework asserts that participants' decisional needs will affect decision quality (informed, values-based choices), which in turn affects actions or behaviour (e.g. delay), health outcomes, emotions (regret, blame), and appropriate use of health services. (See **Glossary of Terms for Ottawa Decision Support Framework**)

APPENDIX 6: OTTAWA DECISION SUPPORT FRAMEWORK: GLOSSARY OF DECISIONAL NEEDS

DECISIONAL NEEDS
DECISION **Type:** class or characteristic of the choice that needs to be made [e.g. developmental transition or clinical options (screen, test, treat, palliate]; number of options, degree of risk/uncertainty, seriousness of outcomes, whether it is irrevocable **Timing:** time frame or urgency with which a decision needs to be made **Stage:** phase of decision making: not thinking about options; considering options; close to selecting an option; taking steps towards implementing option; have already carried out choice. Categories are similar to Prochaska's Stages of Change (1), with one important difference. Deciding not to change is a viable option because often there is no recommended course of action, e.g. amniocentesis. **Leaning:** inclination to choose one option over the other
DECISIONAL CONFLICT uncertainty about course of action to take when choice among options involves risk, loss, regret, challenge to personal life values
KNOWLEDGE & EXPECTATIONS **Knowledge:** cognizance of the health problem or situation, options, and outcomes **Expectation:** perceived likelihood or probability of outcomes of each option
VALUES desirability or personal importance of outcomes of options
SUPPORT & RESOURCES **Others' opinions/ practices:** perceptions of what others decide or what others think is the appropriate choice. This may include a person's spouse, family, peers, and practitioner(s). For practitioners: the patient, professional peers, and personal network **Pressure:** perception of persuasion, influence, coercion from important others to select one option **Role in decision making:** the way a participant is or wants to be involved in decision making; do they prefer to: make the choice themselves after considering opinions; share decision making with another; have others decide after considering their opinion **Experience:** past exposure to the situation, options, outcomes, decision making process **Self-efficacy:** confidence or belief in one's abilities in decision making, including shared decision making **Motivation:** readiness and interest in decision making, including shared decision making **Skill:** abilities in making and implementing a decision **External support**: Available, accessible assets from others that are required to make and implement the decision. Types include: information, advice, emotional support, instrumental help, financial assistance, health & social services. Sources include: social networks, professional networks, support groups, voluntary agencies, and the formal health care, education, and social sectors
PERSONAL & CLINICAL CHARACTERISTICS **Patient:** Age, gender, education, marital status, ethnicity, occupation, locale, diagnosis & duration of condition, health status (physical, emotional, cognitive, social) **Practitioner:** age, gender, ethnicity, clinical education, specialty, practice locale, experience, counselling style
DECISION SUPPORT
PATIENT DECISION AIDS Evidence-based tools to prepare people to participate in making specific and deliberated choices among healthcare options in ways they prefer. They supplement (not replace) clinician's counseling and aid decision making by: a) providing evidence-based information about a health condition, the options, associated benefits, harms, probabilities, and scientific uncertainties; b) helping people to recognize the values-sensitive nature of the decision and to clarify the value they place on the benefits, harms, and scientific uncertainties. Strategies include: describing the options in enough detail that clients can imagine what it is like to experience the physical, emotional, and social effects; and guiding clients to consider which benefits and harms are most important to them; and c) providing structured guidance in the steps of decision making and communication of their informed values with others involved in the decision (e.g. clinician, family, friends).
DECISION COACHING Support provided to people facing a decision by a trained facilitator who is supportive but neutral in the decision. Coaching can be provided face to face (individual, group) or using communication technologies (telephone, Internet). Decision coaching is used alone or in combination with patient decision aids. The strategies may include: a) clarifying decision and monitoring needs; b) facilitating access to evidence-based information, verifying understanding, clarifying values, building skills in deliberation, communication, and accessing support; and c) monitoring and facilitating progress in decision making and decision quality.
DECISION QUALITY
QUALITY OF THE DECISION The extent to which the chosen option best matches informed clients' values for benefits, harms, and scientific uncertainties
QUALITY OF THE PROSESS OF DECISION MAKING The extent to which a person is helped to: a) recognize that a decision needs to be made; b)know about the available options and associated procedures, benefits, harms, probabilities, and scientific uncertainties; c) understand that values affect the decision; d) be clear about which features of the options matter most to them (e.g. benefits, harms, and scientific uncertainties); e) discuss values with their clinician(s); and f) become involved in decision making in ways they prefer.

APPENDIX 7: IPDAS CRITERIA CHECKLIST

I. Content: Does the patient decision aid …

Provide information about options in sufficient detail for decision making?

- ☐ describe the health condition 2.1
- ☐ list the options 2.2
- ☐ list the option of doing nothing 2.3
- ☐ describe the natural course without options 2.4
- ☐ describe procedures 2.5
- ☐ describe positive features [benefits] 2.6
- ☐ describe negative features of options [harms / side effects / disadvantages] 2.7
- ☐ include chances of positive / negative outcomes 2.8

Additional items for tests

- ☐ describe what test is designed to measure 2.9
- ☐ include chances of true positive, true negative, false positive, false negative test results 2.10
- ☐ describe possible next steps based on test result 2.11
- ☐ include chances the disease is found with / without screening 2.12
- ☐ describe detection / treatment that would never have caused problems if one was not screened 2.13

Present probabilities of outcomes in an unbiased and understandable way?

- ☐ use event rates specifying the population and time period 3.1
- ☐ compare outcome probabilities using the same denominator, time period, scale 3.2, 3.3, 3.6
- ☐ describe uncertainty around probabilities 3.4
- ☐ use visual diagrams 3.5
- ☐ use multiple methods to view probabilities [words, numbers, diagrams] 3.7
- ☐ allows the patient to select a way of viewing probabilities [words, numbers, diagrams] 3.8
- ☐ allow patient to view probabilities based on their own situation [e.g. age] 3.9
- ☐ place probabilities in context of other events 3.10
- ☐ use both positive and negative frames [e.g. showing both survival and death rates] 3.13

Include methods for clarifying and expressing patients' values?

- ☐ describe the procedures and outcomes to help patients imagine what it is like to experience their physical, emotional, social effects 4.1
- ☐ ask patients to consider which positive and negative features matter most 4.2
- ☐ suggest ways for patients to share what matters most with others 4.3

Include structured guidance in deliberation and communication?

- ☐ provide steps to make a decision 6.1
- ☐ suggest ways to talk about the decision with a health professional 6.2
- ☐ include tools [worksheet, question list] to discuss options with others 6.3

II. Development Process: Does the patient decision aid …

Present information in a balanced manner?

- ☐ able to compare positive / negative features of options 9.1
- ☐ shows negative / positive features with equal detail [fonts, order, display of statistics] 9.2

Have a systematic development process?

- ☐ includes developers' credentials / qualifications 1.1
- ☐ finds out what users [patients, practitioners] need to discuss options 1.2, 1.3
- ☐ has peer review by patient / professional experts not involved in development and field testing 1.8b
- ☐ is field tested with users [patients facing the decision; practitioners presenting options] 1.4. 1.5

The field tests with users [patients, practitioners] show the patient decision aid is:

- ☐ acceptable 1.6, 1.7
- ☐ balanced for undecided patients 9.3
- ☐ understood by those with limited reading skills 10.6

Use up to date scientific evidence that is cited in a reference section or technical document?

- ☐ provides references to evidence used 11.1
- ☐ report steps to find, appraise, summarise evidence 11.2
- ☐ report date of last update 11.3
- ☐ report how often patient decision aid is updated 11.4
- ☐ describe quality of scientific evidence [including lack of evidence] 11.5b
- ☐ uses evidence from studies of patients similar to those of target audience 11.6

Disclose conflicts of interest?

- ☐ report source of funding to develop and distribute the patient decision aid 7.1, 7.2
- ☐ report whether authors or their affiliations stand to gain or lose by choices patients make after using the patient decision aid 7.3, 7.4

Use plain language?

- ☐ is written at a level that can be understood by the majority of patients in the target group 10.3
- ☐ is written at a grade 8 equivalent level or less according to readability score [SMOG or FRY] 10.4
- ☐ provides ways to help patients understand information other than reading [audio, video, in-person discussion] 10.5

Meet additional criteria if the patient decision aid is Internet based

- ☐ provide a step-by-step way to move through the web pages 8.1
- ☐ allow patients to search for key words 8.2
- ☐ provide feedback on personal health information that is entered into the patient decision aid 8.3
- ☐ provides security for personal health information entered into the decision aid 8.4
- ☐ make it easy for patients to return to the decision aid after linking to other web pages 8.5
- ☐ permit printing as a single document 8.6

Meet additional criteria if stories are used in the patient decision aid

- ☐ use stories that represent a range of positive and negative experiences 5.2
- ☐ reports if there was a financial or other reason why patients decided to share their story 7.5
- ☐ state in an accessible document that the patient gave informed consent to use their stories 5.5

III. Effectiveness: Does the patient decision aid ensure decision making is informed and values based?

Decision processes leading to decision quality. The patient decision aid helps patients to ...

- ☐ recognise a decision needs to be made 12.1
- ☐ know options and their features 12.2. 12.3
- ☐ understand that values affect decision 12.4
- ☐ be clear about option features that matter most 12.5
- ☐ discuss values with their practitioner 12.6
- ☐ become involved in preferred ways 12.7

Decision quality. The patient decision aid ...

- ☐ improves the match between the chosen option and the features that matter most to the informed patient 12.8

APPENDIX 8: COMPLETE DECISION AID

Decision Aid for Treatment of Advanced Pancreatic Cancer

Informed decision making for patients with advanced pancreatic cancer (inoperable, locally advanced, and/or metastatic stage). A tool for patients to help you understand your treatment choices and assist in sharing the decision-making process with your oncologist.

This Decision Aid is right for me if:

-My cancer has spread beyond the pancreas.

-I have not received previous chemotherapy for my cancer.

How can this decision aid help me?

When first diagnosed with cancer, you are faced with a large amount of complicated information about cancer treatments and the particular outcome of each treatment, such as risks and benefits. Sometimes there are several treatment options available to choose from. The amount of information can sometimes seem overwhelming, particularly in a first visit with a medical oncologist. It can be a real challenge to obtain all this information and process it in order to make a treatment choice that best meets your needs in the course of a 1-hour visit with a medical oncologist. Additional support or resources to help guide you to participate in the decision-making process might make your first visit with the oncologist less challenging, and better prepare you to choose your treatment and ask questions you might have. One tool, which can help in this setting, is a patient Decision Aid. Decision Aids are tools that communicate information about treatment options in ways that encourage you to engage with your doctor to choose treatment that is consistent with your needs and what is important to you.

The Decision Aid also outlines both the benefits and harms of the various treatment options. The Decision Aid may make your choice clearer and easier. It

may help you further understand what is more important to you in terms of overall survival, cancer control, avoiding side effects, treating symptoms, quality of life and convenience.

The decision aid is designed to help clarify some of your prioritizations and rankings as well as share these with your doctor. This tool is a guide to help you learn more about both benefits and risks of each option and receive visual feedback about your prioritizations and does not replace the advice of your doctor.

This decision aid is NOT intended to provide you with any medical advice. Please consult your doctor with any questions related to your diagnosis, your treatment options and any other medical related questions you may have.

What is pancreatic cancer?

Pancreatic cancer is a cancer that starts in the cells of your pancreas. A tumour forms when cells begin to grow uncontrollably and develop into lumps or masses of abnormal cells, or tumour cells. The pancreas is a large gland located behind your stomach and is part of both the digestive and hormonal systems. It is responsible for producing digestive juices, which help digest your food. It also produces important hormones such as insulin or glucagon, which helps regulate the sugar levels in your blood.

The Pancreas: Location and Function

- The pancreas is a large gland that is located in your abdomen, behind your stomach.
- The pancreas is part of your digestive system.
- Its function is to make hormones and digestive juices that help the body break down food.
- These juice secretions are deposited into the pancreatic duct.
- The pancreatic duct joins the common bile duct, which carries bile from the liver and empties into the duodenum (the first part of the small intestine).
- The pancreatic juices and bile help digest food in the duodenum after it has left the stomach.
- The pancreas is also part of the hormonal system.
- It makes insulin as well as other hormones that enter into the bloodstream and help your body use or store the energy from the food you eat.
-

Causes of Pancreatic Cancer

Adenocarcinoma of the pancreas affects both men and women and is the second most common gastrointestinal malignancy in North America where 31,000 new cases are diagnosed every

year. According to statistics from the Canadian Cancer Society, approximately 3,400 Canadians are diagnosed with pancreatic cancer yearly.
There is no single cause of pancreatic cancer. Some factors have been shown to increase a person's risk of developing pancreatic cancer:

- **Age:** Most people are diagnosed with pancreatic cancer over the age of 65 years.
- **Obesity:** People who are overweight or have a body mass index greater than 30kg/m2 are at higher risk of developing pancreatic cancer.
- **Diabetes:** A chronic condition caused by an imbalance of blood sugar levels.
- **Chronic pancreatitis** (long-term inflammation of the pancreas)
- **Inherited disorder** (A genetic predisposition to cancer can be passed on from family members):

>*Hereditary pancreatitis*

>*Hereditary non-polyposis colon cancer (HNPCC)*

>*Peutz-Jehgers syndrome*

>*Familial atypical multiple mole melanoma syndrome*

>*Familial breast cancer syndrome.*

Signs and Symptoms

In the earlier stages of the disease, pancreatic cancer does not cause many signs and symptoms. This is because it lies deep in the abdomen where there are less nerve endings that would result in sending pain messages to the brain. As the tumour grows, it may start to spread beyond the pancreas and cause discomfort in the upper abdomen. The most common symptoms of pancreatic cancer are abdominal pain and weight loss.

Pain: Most people will experience pain in the upper abdomen that can spread to the back as a dull ache. Greater pain is experienced with eating.

Weight loss: Weight loss is among the most common symptoms of pancreatic cancer. It can be associated with loss of appetite, diarrhea or feeling full after eating only a small amount of food.

Nausea and vomiting: The pancreas plays a large role in your digestive system. A tumour can cause blockage and discomfort that result in patients feeling nauseous.

Jaundice: Otherwise known as yellowing of the skin and whites of your eyes. The colour of your urine will also be darker. You may become jaundiced if your tumour has blocked the common bile duct (which carries bile from the liver and empties into the duodenum.)

Diagnosis and Staging

Some tests that are used to diagnose pancreatic cancer are:

- Physical examination.
- Stool examination to look for hidden blood.
- Blood tests to evaluate liver function. Sometimes pancreatic cancer can affect the liver and this can be detected on blood tests.
- Abdominal ultrasound uses sound waves to produce a picture of the organ which can locate a tumour.
- CT scan can show a cross section view of the organ. It can pinpoint the size and location of the tumour.
- MRI.
- Biopsy: A small amount of tissue is removed for examination under a microscope.
- Fine needle aspiration: A type of biopsy using a small needle inserted into a mass to withdraw tissue.
- Laparoscopy: A thin instrument is inserted into the abdomen to view the pancreas; used to biopsy and stage the cancer.
- Endoscopic ultrasound: An ultrasound probe is inserted via your mouth under sedation and sound waves are used to see the tumor and take a biopsy.
- Endoscopic retrograde cholangiopancreatography (ERCP): A small camera is inserted via your mouth. This test is done while you are sedated. Images of the pancreatic duct and bile ducts are taken. This is not routinely used for diagnosis, but is often used to help with an obstruction which causes jaundice.

How is my cancer staged?

Stage	Description
IA	Limited to the pancreas, 2cm or smaller in size.
IB	Limited to the pancreas, bigger than 2cm in size.
IIA	Has spread outside the pancreas, but not into large blood vessels, lymph nodes or other parts of the body.
IIB	May have spread outside the pancreas but not into nearby rage blood vessels. It has spread to nearby lymph nodes, but not to other parts of the body.
III	Has spread into nearby large blood vessels, may or may not have spread to nearby lymph nodes, has not spread to other parts of the body.
IV	Has spread to other parts of the body.

What are my treatment options?

Is surgery an option?	Is radiation an option?	Is Chemotherapy an option?
• Surgery is the physical removal of the tumour by a surgeon, if your cancer has not spread anywhere else in your body. • If your cancer has spread to another location outside of the pancreas (liver, lung, bone, stomach) surgery is not a treatment option for you. • While larger tumours can be seen in scans, there can be many other tumours (or masses of abnormal cells) that are too small to see. One way to think of it is that the cancer spreads through the blood like seeds do in the wind and can reach many other areas in your body. • Surgery cannot effectively remove all of these cancerous tumours. • Removing only the visible tumours will cause surgical wounds that require several weeks or sometimes months to heal. This will delay treatment for the other spots that are likely to continue to grow. • Surgery for advanced pancreatic cancer has been unable to improve survival or cure the cancer. • For this reason surgery is usually only used for management of complications, and only if it is necessary. X	• Radiation is the use of high energy particles to damage the DNA of cancer cells over and over again until they disappear. • If your cancer has spread to another body part, radiation therapy is not a treatment option for you. It is a focal treatment that cannot be given to large areas of the body. • While radiation is generally more damaging to cancer cells, it can also damage normal cells. Some normal cells or tissues are particularly sensitive to the negative effects of radiation. • Like surgery, it cannot treat all of the other sites that are already visible or are too small to be seen. • Radiation therapy has been used in combination with chemotherapy in other types of diagnoses of pancreatic cancer. • Radiation therapy for advanced pancreatic cancer has been unable to improve survival or cure the cancer. • Radiation may be helpful for specific symptom management such as pain. X	• Chemotherapy uses drugs to destroy the cancer cells. It can be given as pills or by injection. • Chemotherapy drugs interfere with the ability of cancer cells to grow and spread. • They can also damage healthy cells and over time, and patients can experience side effects from the chemotherapy. • Chemotherapy can be used to target and destroy the spots of cancer in your body that are too small to see and that cannot be surgically removed or treated with radiation therapy. • Chemotherapy is used to treat unresectable and metastatic cases of pancreatic cancer. • For pancreatic cancer, chemotherapy drugs can be given on their own such as Gemcitabine. Other drugs are given together such as FOLFIRINOX. • Chemotherapy can improve symptoms and survival of advanced pancreatic cancer but it cannot cure the cancer. ✓ • Click here to determine whether chemotherapy is an option for you: Decision aid for pancreatic cancer treatment.

What is best supportive care?

Supportive care includes the services needed by people living with or affected by cancer.

This sort of care is intended to meet the following needs of the patient:

- Physical
- Informational
- Emotional
- Psychological
- Social
- Spiritual
- Practical needs during the pre-diagnostic, diagnostic, treatment and follow-up phases.

The main goals of best supportive care include symptom management, improvement of quality of life, and, in some instances, better survival. It includes access to palliative care services.

What are my chemotherapy options?

What is gemcitabine?

• Pronounced: gem-site-ah-been

• Gemcitabine is a single agent chemotherapy made up of 1 drug.

•Has been used as the standard treatment for advanced pancreatic cancer since 1997.

• Has been used in many studies and clinical trials over the past 15 years.

• Associated with some side effects, that are well-managed.

• Often combined with other treatments.

• Also used for other cancer types.

• Although gemcitabine is not associated with as many side effects as other types of chemotherapies or combination therapy such as FOLFIRINOX, the length of survival time and the length of time that the cancer growth is prevented (cancer control) is shorter.

What is FOLFIRINOX?

• Pronounced: fol-fear-in-ox

•FOLFIRINOX is a combination therapy of:

➢Folinic Acid

➢5-Fluorouacil (5FU)

➢Irinotecan

➢Oxaliplatin

•FOLFIRINOX was recently approved in Ontario to treat metastatic pancreatic cancer.

•Clinical trials (Conroy et al. 2011) have compared FOLFIRINOX to Gemcitabine alone and demonstrated that FOLFIRINOX significantly improves overall survival and progression free survival.

•FOLFIRINOX has also been shown to be associated with some risks and toxicities including neutropenia, febrile neutropenia, fatigue, sensory neuropathy and vomiting/diarrhea.

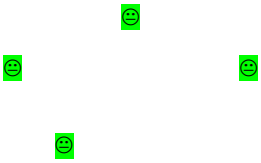
•At this point in time, it is unclear whether the survival benefit of FOLFIRINOX outweighs the added risks and toxicities.

Information guide for deciding between chemotherapy (any) and best supportive care alone:

What is most important to you?	No Chemotherapy-best supportive care alone (Observation and pain management only)	Chemotherapy (Treatment with gemcitabine or FOLFIRINOX)
Survival *Increasing the length of time that I will live.*	-My chances of surviving longer are smaller if treated with best supportive care ☹	My chances of surviving longer are greater if treated with chemotherapy ☺
	Best supportive care alone → Chemotherapy → Survival time	
Cancer Control *Controlling the growth of the cancer so that it doesn't get bigger or so that it doesn't further spread to other parts of my body.*	Cancer will grow at its natural rate- it may continue to spread further into other organs in my body 😐 As my cancer continues to spread, it will cause other symptoms such as pain, fatigue, loss of appetite or constipation ☹ There are medications available to treat the symptoms caused by the growing cancer 😐	Cancer growth is better controlled with chemotherapy ☺ Cancer may**: 1) Shrink (32%) ☺ 2) Stay stable (39%) 😐 3) Keep growing (15%) ☹  The median (middle value) of time of controlled cancer growth is **6.4 months*** **Time (months):** 0----1----2----3----4----5----6--*-7----8 -By controlling cancer growth, chemotherapy can also treat

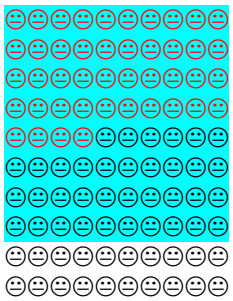
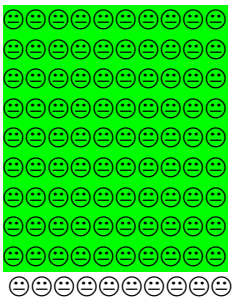
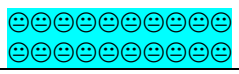
		cancer related symptoms ☺ ***Treatment with FOLFIRINOX*
Avoiding side effects *Depending on whether you chose to have chemotherapy or not, you can experience side effects from the cancer itself or chemotherapy.*	-Avoids side effects from chemo ☺ -Patients may still have symptoms caused by the cancer ☹ -Symptoms from cancer include: -Pain -Decreased appetite -Weight loss -Jaundice (Yellowing of skin) -Decreased energy	Side effects from chemo include: ☹ -Fatigue -Vomiting -Hair loss (alopecia) -Diarrhea -Mouth sores -Sensory neuropathy (tingling sensation) -Sensitive palms of hands/soles of the feet. -Risk of infection
	-Some medications can help manage these side effects such medication for pain, nausea, diarrhea, mouth sores ☺	
Quality of Life *Maintaining a good quality of life and general well-being.*	-Quality of life may get worse over time due to fatigue, loss of appetite, pain, etc. ☹ -Quality of life can be maintained by avoiding side effects from chemotherapy ☺	-Studies show that quality of life worsens slower with chemotherapy than without 😐 -By treating cancer related symptoms such as pain or fatigue with chemotherapy, quality of life can be maintained or improved ☺
	-Hospice care/palliative care can treat all aspects of a patient and family's needs (physical, psychological, social) and can maintain the patient's quality of life ☺	
Treating symptoms *Managing symptoms that are caused by my cancer (pain, fatigue, loss of*	-As your cancer grows, symptoms caused by your cancer may also get worse such as pain, fatigue, weight	-Chemotherapy can treat symptoms caused by your cancer such as pain or fatigue by

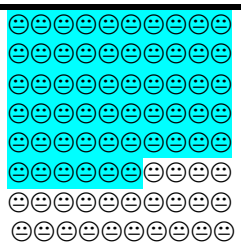
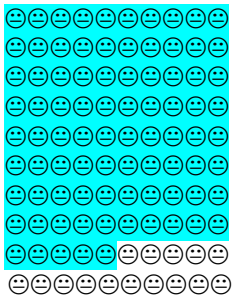
appetite, weight loss.)	loss, etc. ☹ -There are medications available to treat some of the symptoms that are caused by the cancer (e.g. pain medication, anti-depressants) 😐	controlling its growth or shrinking the cancer ☺ -In cases where cancer grows, chemotherapy may not be able to treat the symptoms caused by your cancer and it still may get worse ☹
Convenience *Convenience of treatment with regards to the time that I will have to spend in the hospital, the number appointments I have to make, the time lost at work, time spent travelling and associated costs.*	-Less time will be spent in hospital with fewer visits ☺ -Costs will be less ☺ -Time off of work (if applicable) will not need to be taken as much ☺ -No arrangements for transportation to and from treatments required ☺	-More time will be spent at the hospital (receiving treatment, follow-up visits, getting blood work, getting scans, etc.)😐 -There may be costs associated with receiving treatment (gas, drivers, parking, medication) ☹ -Time from work may need to be taken off ☹ -Patients may need to arrange transportation to and from hospital for chemotherapy treatments. 😐

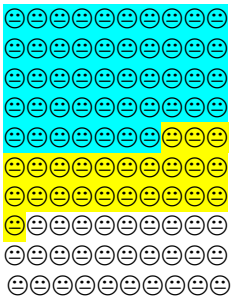
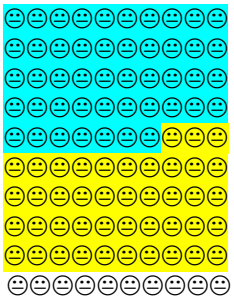
Overall survival statistics		
Best supportive care alone	Gemcitabine	FOLFIRINOX
~40% of patients alive at 6 months.	~58% of patients alive at 6 months.	~76% of patients alive at 6 months.
		
<10% of patients alive at 1 year	<20% of patients alive at 1 year	~48% of patients alive at 1 year
		
<5 % of patients alive at 1.5 years	6 % of patients alive at 1.5 years	~19 % of patients alive at 1.5 years
		
Some people can live for 2 years or longer	<5% of patients alive at 2 years	~10% of patients alive at 2 years
		
Some people can live for 3 years or longer	Some people can live for 3 years or longer	<5% alive at 3 years
		

Reference: Conroy et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. NEJM 2011:364;19 [1817-1825)

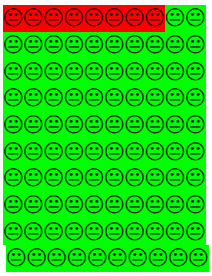
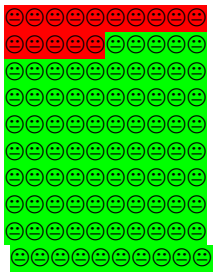
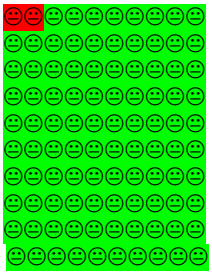
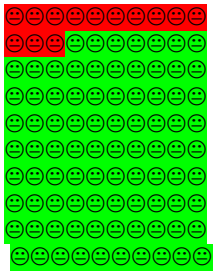
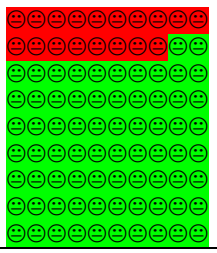
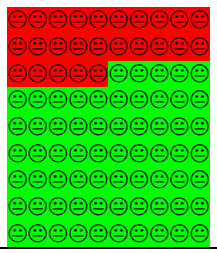
Symptom management for pancreatic cancer comparing chemotherapy (any) with best supportive care. The list of symptoms with definitions are presented in the first column, followed by a general description of the presenting population and the associated statistics and final the differences between the two options in terms of managing the symptom:

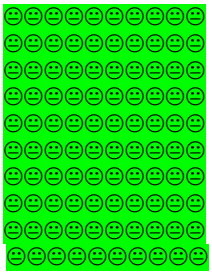
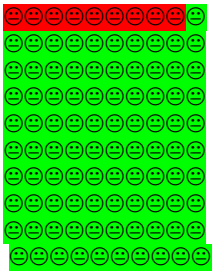
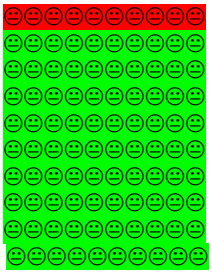
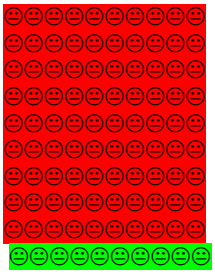
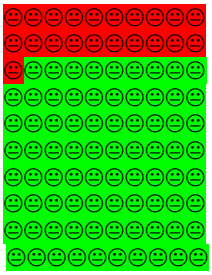
Symptoms	Presentation	SYMPTOM MANAGEMENT	
		Best supportive care alone	Chemotherapy + Best supportive care
Pain • Pain is one of the most common side effects of pancreatic cancer. • Pain syndromes can arise from involvement of important structures surrounding the pancreas. • Pain is the most treatable symptom. • Pain is often the cause of other symptoms such as depression, fatigue, weight loss…	• 80% (80 per 100 patients) will experience pain at presentation (😐). • 44% (😐) of the patients will present with severe pain. • 20% of patients may avoid this 😐	• 90% of patients respond well to oral analgesics and will experience pain relief ☺ • Oral analgesics include: -NSAID and acetomenaphin for **mild pain** (e.g. Tylenol). -Weak opioids for **moderate pain** (e.g. Codeine). -Morphine, oxycodone, hydromorphone, fentanyl for **severe pain**.	• Chemotherapy can relieve pain by shrinking the tumour. • 24% of patients treated with chemotherapy experienced pain relief ☺ + • 90% of patients also respond well to oral analgesics ☺
			+ 
Fatigue • The most common symptom in patients with pancreatic cancer is fatigue. • Fatigue can be caused by other symptoms: - Pain - Weight loss/Cachexia - Depression - Anemia (low red	• 76% of patients experience fatigue at presentation of disease 😐. • 90% of patients present with self-reported cancer-related fatigue. • Important to identify the source of fatigue to treat properly. 	***In both supportive care or chemotherapy treated patients:*** • Treatment of fatigue includes treatment of other symptoms such as pain (see above), weight loss (below), depression (below) and anemia (>50% 😐). • Pain can be managed with pain medication (above). • Anemia can be treated with medication or with red blood cell transfusions. • Exercise routines can help manage fatigue. In chemotherapy patients, exercise can reduce fatigue in 4.2% of patients during treatment and 20.5% post-treatment	

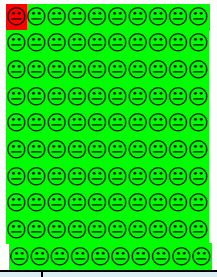
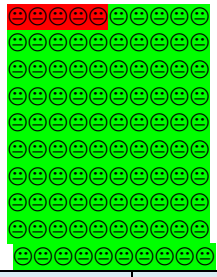
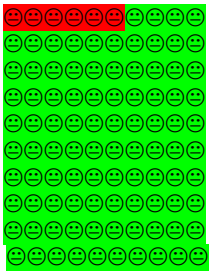
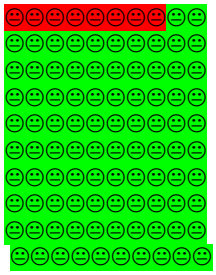
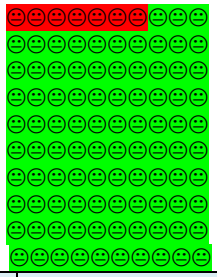
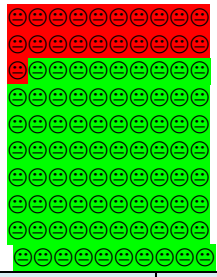
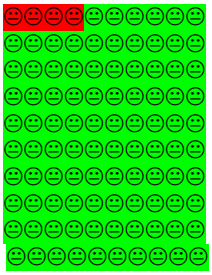
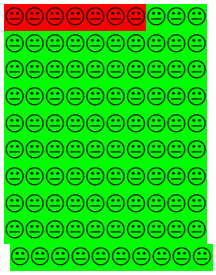
blood cell count) • Fatigue can be a side effect of the cancer itself or of the chemotherapy treatment or both.		Patients can avoid treatment-related fatigue (50%) 😊 	Fatigue is the most common side effect of chemo reported in 18-24% of patients 😐 
Anorexia-Cachexia syndrome *(Loss of appetite and extreme weight loss)* • Cancer related **Cachexia**, which is defined as unintentional weight loss greater than 10% of a patient's body weight, is the most common causes of death in patients with pancreatic cancer. • It is due to abnormal metabolic function caused by your tumour that leads to anorexia (loss of appetite) and extreme weight loss (loss of protein, muscle mass and body fat). • Cachexia contributes to depression and is a predictive factor of poor quality of life.	• 85% of all pancreatic cancer patients develop cachexia 😐. • Patients lose a median of 14.2% of their initial body weight by the time of diagnosis. • Best cure for cachexia is removal of the tumour which is only possible in ~10% of resectable cases. 	• As the tumour grows and spreads into the body, anorexia-cachexia can get worse. • Choosing not to have cancer treatment can help avoid further side effects that can worsen cachexia. ***In both supportive care or chemotherapy treated patients:*** • Pharmacological intervention can help manage weight loss and cachexia symptoms: - Omega-3 fatty acid supplements can increase appetite, decrease weight-loss and improve quality of life. - Dexamethasone can increase appetite. - Magistrol causes weight gain (15% of patients) - Eicosapentaenoic acid helps patients maintain their muscle mass. - Other drugs are being developed to help treat cancer-related cachexia (anti IL-6 antibodies or Selective Androgen Receptor Modulators, etc)	• Cachexia is associated with lower tolerance of chemotherapy and dose adjustments are often required. • Can be worsened by other treatment related symptoms (diarrhea, nausea, vomiting). • There are good drugs available to treat nausea, vomiting and diarrhea.
Depression	• Depression has been diagnosed in 47😐-71😐%	• Patients who chose not to have chemotherapy	• Patients receiving chemotherapy can

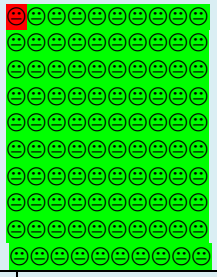
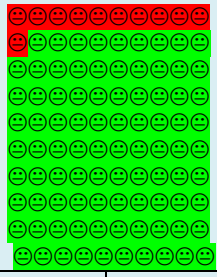
• Depression is more common in patients with pancreatic cancer than in patients with any other type of cancer. • Depression is linked to pain and fatigue, which are other common symptoms caused by pancreatic cancer (above).	‘ Of patients who present with pancreatic cancer. 	treatment may avoid becoming depressed from chemotherapy side effects and treatment related stress.	experience higher levels of depression due to side and stress from treatment.
		In both supportive care or chemotherapy treated patients: _____ _____ • Treatment of other symptoms (pain, weight loss, fatigue) can help treat depression. • Anti-depressants can help manage or treat depression (large selection of anti-depressants that have all been shown to be effective). • Pscyhotherapy and cognitive therapy have been shown to treat depression in cancer patients. • Depression can be managed with alternative intervention (acupuncture, yoga, social groups…)	
Jaundice • Jaundice can be recognized by the yellowing of the skin and of the eyes. • Jaundice can also cause dark urine and light-colored stools. • When the tumour blocks the flow of bile from the gallbladder into the intestine, bilirubin will spill into your blood causing you to turn yellow.	• 47% of patients with pancreatic cancer will be jaundiced at presentation 😐. • 90% of pancreatic cancer patients will have jaundice during some phase of their illness 😐. 	***In both supportive care or chemotherapy treated patients:*** • Relief of biliary obstruction can decrease symptoms, improve quality of life and increase overall survival. • The most common treatment for biliary obstruction is a stent (small tube inserted into your biliary duct to keep it open). • The stent is placed using a procedure called ERCP (endoscopic retrograde cholangiopancreatography). • Surgical removal or bypass can also be used to remove the blockage. • Both procedures are effective. • There are some complications associated with both procedures including increased risk of infection, bleeding or inflammation of pancreas and other organs. (pancreatitis, cholectitis, cholangitis).	

What is most important to you?	Gemcitabine (Single Agent chemotherapy)	FOLFIRINOX (Combination of 5-Fluourouacil, Leucovorin, Irinotecan and Oxaliplatin)
Survival *Increasing the length of time that I will live*	-Patients treated with gemcitabine have greater chance of surviving longer than patients with best supportive care alone. ☺ -Median survival time in patients treated with gemcitabine is ~1.5 times shorter than in patients treated with FOLFIRINOX	-Patients treated with FOLFIRINOX have greater chance of surviving longer than patients treated with gemcitabine ☺ -Median survival time in patients treated with FOLFIRINOX is ~1.5 times longer than in patients treated with gemcitabine ☺
Cancer Control *Controlling the growth of the cancer so that it doesn't get bigger or so that it doesn't further spread to other parts of my body.*	-Cancer has a higher risk of growing in patients treated with gemcitabine than in patients treated with FOLFIRINOX. Cancer may: 1) Shrink (9%) ☺ 2) Stay stable (42%) 😐 3) Keep growing (35%) ☹  The median (middle value) progression free survival time is **3.3 months*** **Time (months):**	-Cancer growth is better controlled in patients treated with FOLFIRINOX. Cancer may: 1) Shrink (32%) ☺ 2) Stay stable (39%) 😐 3) Keep growing (15%) ☹  The median (middle value) progression free survival time is **6.4 months***

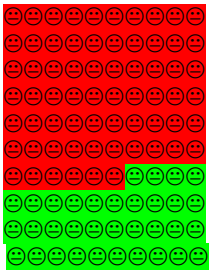
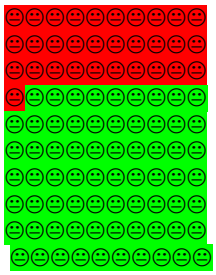
		0----1----2----3-*---4---5----6----7----8		Time (months): 0----1----2----3----4----5----6--*-7----8	
Adverse Events and Side effects	**ADVERSE EVENTS***	-Less toxicities in patients treated with Gemcitabine ☺ *(See below for complete break down of all side effects)*		-More toxicities in patients treated with FOLFIRINOX ☹ *(See below for complete break down of all side effects)*	
Chemotherapy is associated with important side effects that can affect the quality of life and prognosis of a patient. *The side effects, or adverse events, listed are those that occur in more than 5% of patients.* *-There are good* *medications available to treat and help control some of these side effects such as nausea, diarrhoea or hematologic side effects.*	**Vomiting** *Nausea and vomiting usually well-controlled.				
		-8 % of patients experience this ☹	-92% of patients avoid this ☺	-15 % of patients experience this ☹	-85% of patients avoid this. ☺
	Diarrhea *Diarrhea is usually well-controlled.				
		-2% of patients experience this ☹	-98% of patients avoid this ☺	-13% of patients experience this ☹	-87% of patients avoid this. ☺
	Fatigue				

Numbers presented correspond to **grade 3 AND **grade 4** adverse events only.* ***Grade 3:** Severe or medically significant event requiring hospitalization, but not life-threatening.* ***Grade 4:** Life-threatening requiring urgent intervention.* **All numbers are rounded to the nearest 10th.*					
		-18% of patients experience this	-82% of patients avoid this 	-24% of patients experience this	-76% of patients avoid this. 
	Sensory Neuropathy (Grade 3 or 4 adverse event) *-Numbness and tingling of hands and feet.* *-Changes in hearing* *-Sensitivity to cold temperatures.* *-Can cause permanent damage.*				
		-0% of patients experience this	-100% of patients avoid this 	-9% of patients experience this	-91% of patients avoid this. 
	Sensory Neuropathy (Any grade) *Certain chemotherapy drugs such as Oxaliplatin (in FOLFIRINOX) can affect your hearing and sensation in your fingers.				
		-10% of patients experience this	-90% of patients avoid this	-90% of patients experience this	-10% of patients avoid this
	Neutropenia (*Low White blood cell count)*				
		-21% of patients experience this	-79% of patients avoid this 	-46% of patients experience this	-54% of patients avoid this. 

**Hair Loss was not reported as a serious (grade 3 or 4) adverse event and is an occasional side effect in patients treated with either gemcitabine or FOLFIRINOX.*	**Febrile neutropenia** *(Fever and infection in patients with neutropenia)*				
		-1% of patients experience this	-99% of patients avoid this	-5% of patients experience this	-95% of patients avoid this.
	Anemia *(Low red blood cell count, low iron in blood)*				
		-6% of patients experience this	-94% of patients avoid this	-8% of patients experience this	-92% of patients avoid this.
	Elevated level of ALT (Enzyme *associated with liver function)*				
		-7% of patients experience this	-93% of patients avoid this	-21% of patients experience this	-79% of patients avoid this.
	Thrombo-embolism *(Formation of blood clot in your blood vessels that prevents blood from flowing)*				
		-4% of patients experience this	-96% of patients avoid this	-7% of patients experience this	-93% of patients avoid this.

<table>
<tr><td rowspan="2"></td><td rowspan="2">Hair loss*
(ALOPECIA)
Hair will grow back after stopping treatment.</td><td colspan="2">  </td><td colspan="2">  </td></tr>
<tr><td>-1% of patients experience hair loss or thinning of the hair 😞</td><td>-99% of patients avoid this 😐</td><td>-11% of patients experience hair loss or thinning of the hair 😞</td><td>-89% of patients avoid this 😐</td></tr>
<tr><td rowspan="2">Quality of Life

Maintaining a good quality of life and general well-being.

Scores for quality of life are obtained from a 30-item questionnaire (EORTC QLQ-C30) that patients fill out about their general well being and quality of life. It includes questions about their physical (energy levels, fatigue, nausea, constipation, etc.), psychological (anxiety, depression, moodiness) and social (friendships, relationships) well-being.</td><td colspan="2">-Quality of life deteriorates faster in patients treated with gemcitabine 😑
  </td><td colspan="2">-Quality of life deteriorates slower in patients treated with FOLFIRINOX ☺
  </td></tr>
<tr><td>At 6 months 66%(😞) of patients had a decrease in quality of life scores from scores at baseline.</td><td>33% (😐) of patients did not have a definitive decrease of quality of life scores from scores at baseline.</td><td>At 6 months 31% (😞) of patients had a decrease in quality of life scores from scores at baseline.</td><td>69% (😐) of patients did not have a definitive decrease of quality of life scores from scores at baseline.</td></tr>
<tr><td>Treating symptoms
Managing symptoms that are caused by my cancer (pain, fatigue, loss of appetite, weight loss.)</td><td colspan="2">Gemcitabine can treat symptoms caused by your cancer such as pain or fatigue. 😑</td><td colspan="2">Cancer has a higher chance of shrinking or staying stable in patients treated with FOLFIRINOX and can result in treating your cancer-related symptoms ☺.</td></tr>
</table>

Convenience *Convenience of treatment with regards to the time that I will have to spend in the hospital, the number appointments I have to make, the time lost at work, time spent travelling and associated costs (if applicable).*	-Gemcitabine is a single chemotherapy drug. -Gemcitabine is given as an intravenous infusion (medication is given to you through you're a small tube that is inserted into your veins). -Infusion lasts approximately **30 minutes** at the hospital. ☺ -No continuous infusions required at home. -Less time at the hospital will be spent (30 minutes) but more frequent consecutive visits (once a week for 7 weeks) ☺ -Intravenous drugs can be infused into your body through a picc line (a long, small, and flexible tube inserted into a vein in your upper arm) or through a Portacath (a small bubble inserted under your skin close to your collar bone where a long flexible tube will be inserted into the bubble and will release the drugs through your central vein). -Your treatment is usually given with other drugs that help treat and prevent nausea, and driving home is not recommended as these drugs can make you feel drowsy. Transportation must be arranged to and from hospital. 😐 -Less time lost at work (only 30 minute treatments) ☺	-FOLFIRINOX is made up of 4 different chemotherapy drugs (5-Fluorouacil, Irinotecan, Leucovorin and Oxaliplatin). -These drugs are given as intravenous infusions at the hospital. One of the drugs (5-Fluorouacil) is given as a continuous infusion over a 46-hour time period at your home. -Total infusion time in hospital is: **2 hours** (Oxaliplatin) + **2 hours** (Leucovorin and Irinotecan (1.5 hours) + **15 minutes** (5Fluorouacil) = **4 hours and 15 minutes** 😐 -You will be given a pouch that carries a bottle with a balloon inside which will be slowly injecting the chemotherapy into your blood system over a 46 hour (2 day) time period. The pouch can be worn around your waist and the tubes will be hidden beneath your shirt where they will be inserted into your picc-line or Portacath (recommended). -Your treatment is usually given with other drugs that help treat and prevent nausea, and driving home is not recommended as these drugs can make you feel drowsy. Transportation must

Treatment schedules (Gemcitabine or FOLFIRINOX) are repeated for 6-12 cycles (up to 6 months) or until patient wishes to stop, until further cancer progression, severe adverse events or otherwise recommended by your oncologist. Patients can take a break from treatment any time and doses can be adjusted and reduced if patient is experiencing side effects.	**Cycle 1*:** *30-minute treatment (|) on day 1 of every week for 7 weeks. NO treatment (0) on day 1 of 8th week. Cycle 1 is then finished. Patients are re-assessed and then continue on to cycles 2, 3, 4, 5, 6, etc.* **Week**: 1 2 3 4 5 6 7 8 | | | | | | | O **Cycle 2, 3, 4, 5, 6…*** *30-minute treatment (|) on day 1 of every week for 3 weeks. NO treatment (0) on day 1 of 4th week. Cycle 2 is then repeated.* **Week**: 1 2 3 4 | | | O	be arranged to and from hospital. 😐 -More time required to be taken off work (Treatments >4 hours long) ☹ **Cycle 1, 2, 3, 4, 5, 6…** *4.25-hour treatment (|) on day 1 of every second week. Treatment on Day 1 of week 1. No treatment (0) on day 1 of week 2. Cycle repeats every 15 days (3 days of treatment, 11 days off). A nurse will visit your home on the 3rd day of every treatment week to take your fluorouracil slow infusion pump off**.* **Week**: 1** 2 | 0

APPENDIX 9: INFORMATION SHEET AND CONSENT FORM

Information Sheet and Consent Form

Study name: Decision Aid for Patients with Advanced Pancreatic Cancer

Primary Investigator: Derek Jonker, Medical Oncology, The Ottawa Hospital Cancer Centre,

Introduction

You are being asked to participate in this research project because you have been diagnosed with advanced pancreatic cancer at The Ottawa Hospital Cancer Centre (TOHCC). Research studies include only participants who choose to take part.

This document describes the purpose, procedures, benefits, discomforts and risks associated with this study, as well as your rights should you decide to participate in the study. Before agreeing to participate, it is important for you to understand the study.

Please read this Patient Information Sheet and Consent Form carefully and ask as many questions as you like before deciding whether to participate in this research study. You can discuss this decision with your family, friends and your health-care team. Please ask the study staff to explain any words in this document that you do not understand, and make sure all your questions have been answered to your satisfaction before signing this study information and consent form.

Background, Purpose and Design of the Study

When first diagnosed with cancer, you are faced with a large amount of complicated information about cancer treatment and the outcome of that treatment, such as risks and benefits. Sometimes there are several treatment options available to choose from. The amount of information can sometimes seem overwhelming, particularly in a first visit with a medical oncologist. It can be a real challenge to obtain all this information and process it in order to make a treatment choice that best meets your needs in the course of a 1 hour visit with a medical oncologist. Additional support or resources to help guide you to participate in the decision-making process might make your first visit with the oncologist less challenging, and better prepare you to choose your treatment and ask questions you might have. One tool, which can help in this setting, is a patient Decision Aid.

Decision Aids are tools that communicate information about treatment options in ways that encourage you to engage with your doctor to choose treatment that is consistent with your needs and what is important to you. The Decision Aid also outlines both the benefits and harms of the various treatment options. The Decision Aid may make your choice clearer and easier.

The doctors involved with this research study hope that the use of a Decision Aid will improve communication between you and your doctor and assist you in choosing between your treatment options, including supportive care, gemcitabine and FOLFIRINOX. A Decision Aid may also assist your doctor in better understanding your preferences and goals.

Study Procedures and or Description of Treatment

If you agree to participate in this study, you will be asked to complete a ten-item baseline questionnaire prior to receiving the Decision Aid. This questionnaire will be completed once at the beginning of the study period and a second time after your first consultation with the medical oncologist. The questionnaire will ask you general questions about your knowledge and understanding of the available treatments for your cancer. This should take five minutes to complete. Once you have completed this questionnaire, the clinical research assistant will provide you with the website address to go through the Decision Aid.

On the website, you can take as little or as much time as you need to review the information provided about your treatment options and their associated benefits and risks. You may then use the Decision Aid to help you decide which treatment is best for you based on what is most important to you. You can go through this alone or with your family and friends. You may then share the results that will be given to you after you complete the Decision Aid with your medical oncologist in order to participate in the decision making process. It is important that you understand that this is only an aid to help you communicate and be better informed about your treatment options and is not a final decision. Your answers will only be shared with your medical oncologist should you chose to do so. After your consultation with the medical oncologist, you will be asked to rate the Decision Aid using a ten item questionnaire provided to you by the study personnel and assess its helpfulness in your decision making process. This questionnaire will take between five and ten minutes to complete.

The total length of time required for your participation at the hospital will be twenty minutes, which involves the information and consent period and first questionnaire. You may then spend as much or as little time at home or in the waiting room to go through the Decision Aid prior to your consultation with the medical oncologist.

Study Duration

Your participation will begin the date you agree to participate in the study, and your active involvement will end after you complete the 20 minute questionnaire following your consultation with the medical oncologist. Following your consultation, data about your treatment will be collected from your patient record for a period of 6 months.

Possible Side Effects and/or Risks

There is the risk that you may be sensitive to some of the questions that are included in the questionnaire. We will distribute a pamphlet that directs you to the psychosocial oncology program at our centre, as well as the contact information of one of the social workers, should you feel any distress. You can contact the psychosocial staff at any time.

Benefits of the Study

You may not directly benefit from this study. Using the Decision Aid will give you access to information about the treatment options available to you. This might help you through the decision making process, and make your first consultation with the medical oncologist less overwhelming and more helpful.

Study Withdrawal

You have the right to withdraw from this study at any time. Your decision to stop participating, or to choose not to answer particular questions, will not affect your current or future care at The Ottawa Hospital Cancer Centre. If you decide to withdraw, you should discuss this with the study doctor or nurse before you stop the study. In the event that you withdraw from the study, all associated data that was collected will be immediately destroyed wherever possible.

Study Costs

You will not be paid to participate in this research study.

Confidentiality

All personal health information will be kept confidential, unless release is required by law. Representatives of The Ottawa Hospital Research Ethics Board, as well as the Ottawa Hospital Research Institute may review your original medical records under the supervision of Dr. D Jonker's staff for audit purposes.

You will not be identifiable in any publications or presentations resulting from this study. No identifying information will leave The Ottawa Hospital. All information that leaves the hospital will be coded with an independent study number.

The link between your name and the independent study number will only be accessible by study staff. The link and study files will be stored separately and securely. Both files will be kept for a period of 10 years after the study has been completed. All paper records will be stored in a locked file and/or office. All electronic records will be stored on a hospital server and protected by a user password, only accessible by Dr. D Jonker and/or his staff. At the end of the retention period, all paper records will be disposed of in confidential waste or shredded, and all electronic records will be deleted. Your clinic doctors and nurses will not have access to any of your questionnaire answers, as these will be coded only with your study number and collected and processed only by the research assistant.

Voluntary Participation

Your participation in this study is voluntary. If you choose not to participate, your decision will not affect the care you receive at this Institution at this time, or in the future. You will not have any penalty or loss of benefits to which you are otherwise entitled.

New Information About the Study

You will be told of any new findings during the study that may affect your willingness to continue to participate in this study. You may be asked to sign a new consent form.

Questions about the Study

If you have any questions about this study, please contact Dr. Derek Jonker or Gillian Gresham. The Ottawa Hospital Research Ethics Board (OHREB) has reviewed this protocol. The OHREB considers the ethical aspects of all research studies involving human participants at The Ottawa Hospital. If you

have any questions about your rights as a research participant, you may contact the Chairperson of the Ottawa Hospital Research Ethics Board at 613-798-5555, extension 14902.

Decision Aid for Patients with Advanced Pancreatic Cancer

Consent to Participate in Research

I understand that I am being asked to participate in a research study evaluating the use of patient decision aid in the clinic. This study has been explained to me by_____.

I have read this 4-page Patient Information Sheet and Consent Form (or have had this document read to me). All my questions have been answered to my satisfaction. If I decide at a later stage in the study that I would like to withdraw my consent, I may do so at any time.

I voluntarily agree to participate in this study.

A copy of the signed Information Sheet and/or Consent Form will be provided to me.

Signatures

_____

Participant's Name (Please Print)

_____ _____

Participant's Signature Date

Investigator Statement (or Person Explaining the Consent)

I have carefully explained to the research participant the nature of the above research study. To the best of my knowledge, the research participant signing this consent form understands the nature, demands, risks and benefits involved in participating in this study. I acknowledge my responsibility for the care and well being of the above research participant, to respect the rights and wishes of the research participant, and to conduct the study according to applicable Good Clinical Practice guidelines and regulations.

_____

Name of Investigator/Delegate (Please Print)

_____ _____

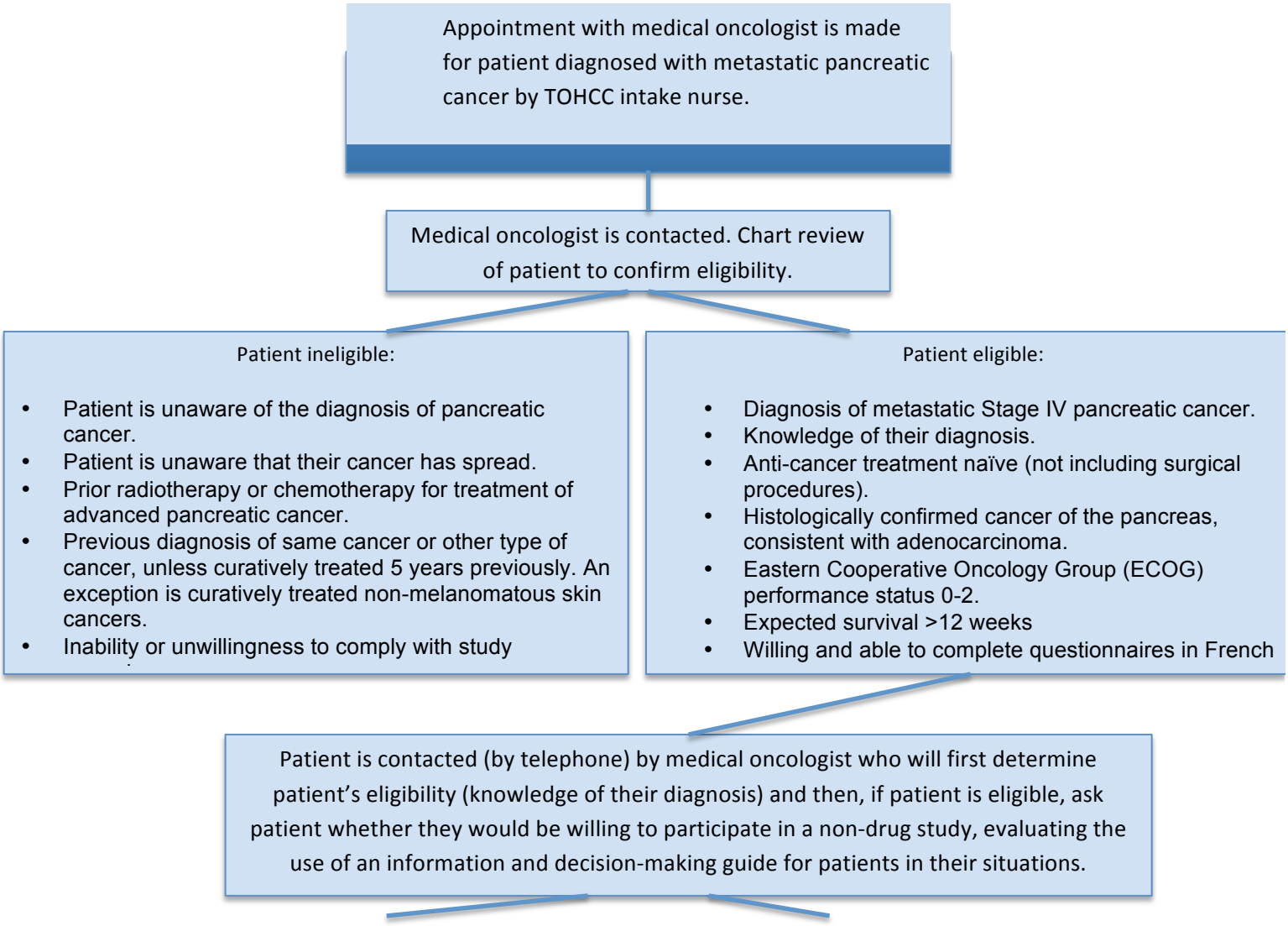
Signature of Investigator/Delegate Date

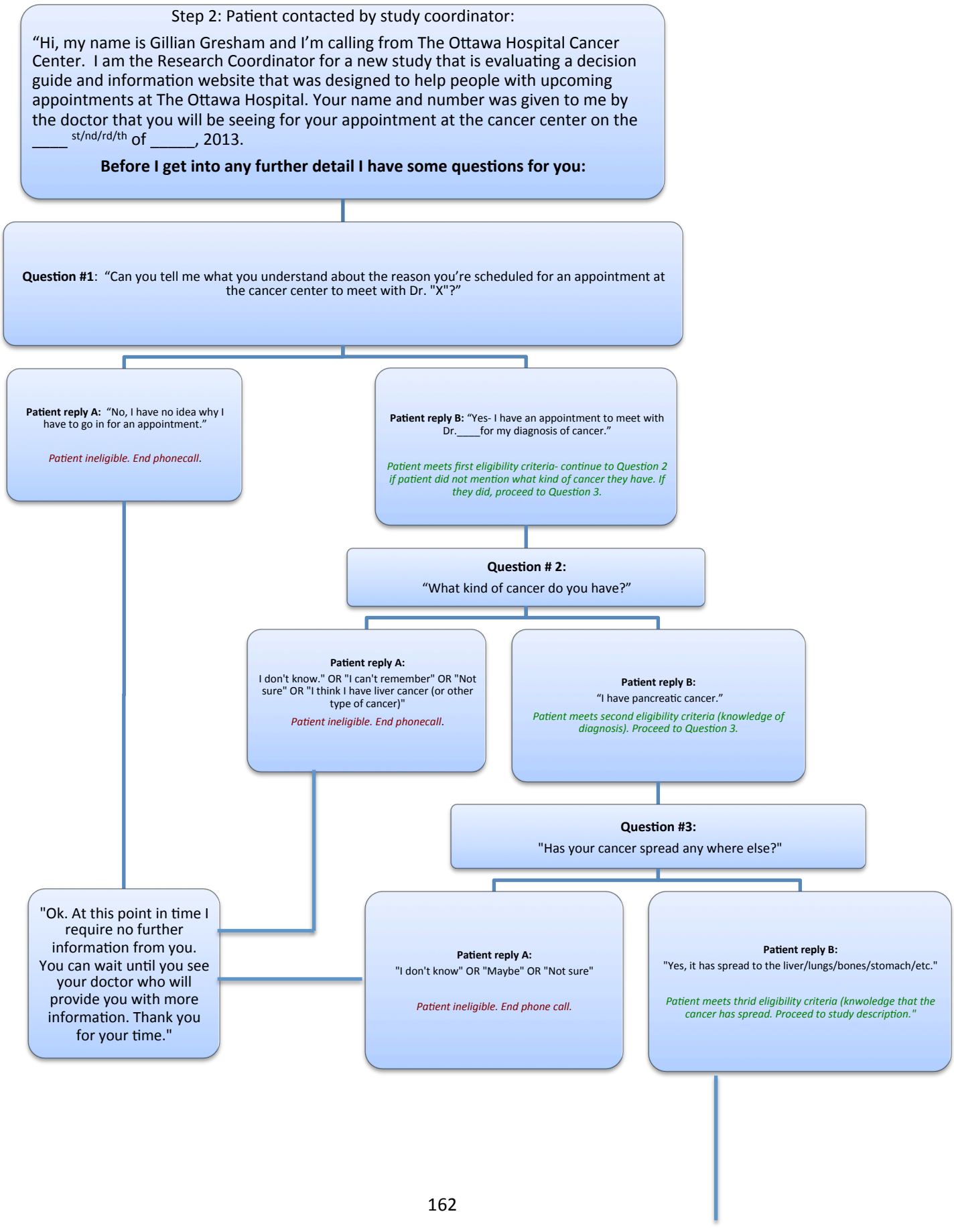
APPENDIX 10: Phone call Script

Patient recruitment by phone call:

Please Note: The study coordinator will NOT be disclosing any information whatsoever to the patient regarding their diagnosis, medical situation and any other information in their records. The coordinator will NOT review the patient's chart prior to the phone call. The only information they will have is their contact information, appointment date with the medical oncologist, and eligibility (advanced pancreatic cancer) passed on to them by the intake nurse at The Ottawa Hospital Cancer Center.

Step 1: Patient contact by medical oncologist asking permission for patient to be approached by study personnel.




Step 2: Patient contacted by study coordinator:
"Hi, my name is Gillian Gresham and I'm calling from The Ottawa Hospital Cancer Center. I am the Research Coordinator for a new study that is evaluating a decision guide and information website that was designed to help people with upcoming appointments at The Ottawa Hospital. Your name and number was given to me by the doctor that you will be seeing for your appointment at the cancer center on the ____ st/nd/rd/th of _____, 2013.
Before I get into any further detail I have some questions for you:
Question #1: "Can you tell me what you understand about the reason you're scheduled for an appointment at the cancer center to meet with Dr. "X"?"
Patient reply A: "No, I have no idea why I have to go in for an appointment."
Patient ineligible. End phonecall.
Patient reply B: "Yes- I have an appointment to meet with Dr.____for my diagnosis of cancer."
Patient meets first eligibility criteria- continue to Question 2 if patient did not mention what kind of cancer they have. If they did, proceed to Question 3.
Question # 2:
"What kind of cancer do you have?"
Patient reply A:
I don't know." OR "I can't remember" OR "Not sure" OR "I think I have liver cancer (or other type of cancer)"
Patient ineligible. End phonecall.
Patient reply B:
"I have pancreatic cancer."
Patient meets second eligibility criteria (knowledge of diagnosis). Proceed to Question 3.
Question #3:
"Has your cancer spread any where else?"
"Ok. At this point in time I require no further information from you. You can wait until you see your doctor who will provide you with more information. Thank you for your time."
Patient reply A:
"I don't know" OR "Maybe" OR "Not sure"
Patient ineligible. End phone call.
Patient reply B:
"Yes, it has spread to the liver/lungs/bones/stomach/etc."
Patient meets thrid eligibility criteria (knwoledge that the cancer has spread. Proceed to study description."

Study Description:

"We have a study available for people in your situation. It is a process that is designed to help you better understand the information about your diagnosis and treatment options and will allow you to participate in the decision making process that you share with your physician. Normally, the information in this tool is given to you at the time of your first appointment with the medical oncologist. However, these visits can be very busy, sometimes overwhelming and difficult to take in all at once. The decision aid will allow you to review your options, learn more about both the benefits and risks of these options and discuss with your family and friends or think over by yourself before you see the doctor so that you are better prepared for the visit. If you chose to participate in this study, we will need to arrange a visit at the hospital at a convenient time for you (perhaps the same day of another appointment such as blood draw or imaging) in order to go over the informed consent form and have you sign it. At this time, I will also provide you with the link to a website only available to those who participate in this study, that will guide you through your decision making process. I will also ask you to answer ten short questions before you leave that day. Aside from this meeting, and the time that you decide to take to read through the information and use the decision guide at home, you will only have to visit the website once more after your appointment with "Dr. X" your medical oncologist to rate this guide by answering three short questionnaires. These answers will help us to improve the guide and make the experience better for future patients. Once you have rated this decision guide after your visit with Dr._____ on the _____th of _____, 2013, your participation in the study will be completed.

I am happy to go over this with you at the time of our meeting as well where I can show you how to use the guide on the hospital computer. Please remember that your participation in this study is completely voluntary and has no relation or influence whatsoever on the treatment you will receive, your care here at the hospital with any of the physicians and any final treatment decision. This is simply to provide you with the opportunity to be a part of the decision making process, to share this with your doctor if you would like and to be better informed about your diagnosis, the treatment options and what is most important to you, before you see the doctor. Do you have any questions for me?

Thank you for your consideration. If you would like to think about this first, you can call me back at (613)____-_____ with an answer and meeting time."

APPENDIX 11: OHREB approval letter

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

THE OTTAWA HOSPITAL
L'HÔPITAL D'OTTAWA

uOttawa

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches

[redacted]

March 20, 2013

Dr. Derek Jonker
The Ottawa Hospital Cancer Centre
Division of Medical Oncology
[redacted]

Dear Dr. Jonker:

Re: Protocol # [redacted] **Informed Decision Making for Patients with Advanced Pancreatic Cancer Considering Chemotherapy: Evaluation of a Clinical Decision Aid for Patients.**

Protocol approval valid until - March 19, 2014

Thank you for the revised documents received March 8, 2013. I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made to the protocol or the consent form without the OHREB's review and approval.

Approval is for the following documents:
- Protocol dated December 16, 2012
- English and French Information Sheet and Consent Forms both dated March 1, 2013
- English Telephone Script received January 17, 2013
- French Telephone Script received March 8, 2013
- English and French Brochure received March 8, 2013
- English Chemotherapy Decision Aid received December 29, 2012
- English "Rate this Decision Aid" document (acceptability 1) received December 29, 2012
- English "Decision Aid Acceptability" document (acceptability 2) received December 29, 2012
- English Traditional Decisional Conflict Scle (DSC) (appendix 5) received December 29, 2012
- English "Is Chemotherapy Right for Me?" document (Part 1 and 2) both received December 29, 2012
- English Overall Survival document received December 29, 2012
- English Folfirinoxda document received December 29, 2012

The validation date should be indicated on the bottom of all consent forms and information sheets (see copy attached). If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Yours sincerely,

[redacted]

Francine F-A. Sarazin, Ph.D., C.Psych.
Vice-Chairperson
Ottawa Hospital Research Ethics Board

[redacted]

Appendix 12: Decision Aid Feasibility questionnaire

Rate this decision aid

Please indicate your opinion about the effect of this educational material by answering the following questions:
Please enter the Study Participant Number that the research assistant has assigned to you in the space below: *

Note: This number is random and not linked to your personal information. All your answers will remain confidential

Did this educational material help you recognize that a decision needs to be made? *
[1=Not at all 2=A little 3=Somewhat 4=Quite a bit 5=A great deal]

	1	2	3	4	5	
Not at all						A great deal

Did this educational material prepare you to make a better decision? *
[1=Not at all 2=A little 3=Somewhat 4=Quite a bit 5=A great deal]

	1	2	3	4	5	
Not at all						A great deal

Did this educational material help you think about the pros and cons of each option? *
[1=Not at all 2=A little 3=Somewhat 4=Quite a bit 5=A great deal]

	1	2	3	4	5	
Not at all						A great deal

Did this educational material help you think about which pros and cons are most important to you? *
[1=Not at all 2=A little 3=Somewhat 4=Quite a bit 5=A great deal]

	1	2	3	4	5	
Not at all						A great deal

Did this educational material Help you know that the decision depends on what matters most to you? *
[1=Not at all 2=A little 3=Somewhat 4=Quite a bit 5=A great deal]

	1	2	3	4	5	
Not at all						A great deal

Did this educational material help you think about how involved you want to be in this decision? *

[1=Not at all 2=A little 3=Somewhat 4=Quite a bit 5=A great deal]

	1	2	3	4	5	
Not at all						A great deal

Did this educational material help you identify questions you want to ask your doctor? *

[1=Not at all 2=A little 3=Somewhat 4=Quite a bit 5=A great deal]

	1	2	3	4	5	
Not at all						A great deal

Did this educational material prepare you to talk to your doctor about what matters most to you? *

[1=Not at all 2=A little 3=Somewhat 4=Quite a bit 5=A great deal]

	1	2	3	4	5	
Not at all						A great deal

Did this educational material prepare you to share the decision making with your doctor about which treatment you would like to receive? *

[1=Not at all 2=A little 3=Somewhat 4=Quite a bit 5=A great deal]

	1	2	3	4	5	
Not at all						A great deal

APPENDIX 13: Decision Aid Acceptability questionnaire

Decision Aid Acceptability

My thoughts on this educational website on treatment options for advanced pancreatic cancer.

* Required

Please enter the Study Participant Number that the research assistant has assigned to you in the space below: *

Note: This number is random and not linked to your personal information. All your answers will remain confidential.

How did the computer-based decision aid affect you?

- ○ Using a computer had a positive effect on me- I liked navigating through the different links on the website.
- ○ Using a computer had a negative effect on me- I would have preferred this information in a paper brochure.
- ○ Using a computer had neither a positive or negative effect on me-I am indifferent to the type of technology used.
- ○ I preferred using a computer but needed someone to help me navigate through the website

Question 1 *

Please rate each section by selecting 'poor', 'fair', 'good', or 'excellent' to show what you think about the way the information was presented to you on this website.

	Poor	Fair	Good	Excellent
Information on pancreatic cancer	○	○	○	○
Information on treatment options available for pancreatic cancer	○	○	○	○
Information on the benefits associated with each type of treatment	○	○	○	○
Information on the risks and side effects of the different treatment options	○	○	○	○
The decision aid to chose between chemotherapy and best supportive care alone	○	○	○	○
The decision aid to chose between FOLFIRINOX and Gemcitabine	○	○	○	○

Question 2 *
How difficult was it for you to navigate this website and find the information you were looking for?

- Not difficult at all
- Somewhat difficult
- Very difficult

Question 3 *
The amount of information included in this website was (select one that applies)

- Too little information
- Too much information
- Just right

Question 4 *
I found the information in the website

- Slanted towards choosing chemotherapy (versus best supportive care alone)
- Slanted towards choosing FOLFIRINOX (versus Gemcitabine)
- Objective and balanced when presenting the different treatment options

Quesiton 5 *
Which part of the decision aid did you find most useful in your decision making process (select one that applies):

- Decision aid for choosing chemotherapy versus best supportive care alone
- Decision aid for choosing FOLFIRINOX versus Gemcitabine
- Both were useful towards my decision making process

Question 6 *
Were you aware of the different treatment options available to you before using this decision aid?

- Yes
- No
- Unsure

Question 7
How did your visit with your doctor impact your decision?

- After speaking with my doctor, I changed my mind about the decision I had made
- After speaking with my doctor, I felt more confident about the decision I had made
- I did not make a decision- I planned on following my doctor's treatment plan for me.

Question 8 *
Would you recommend this educational tool and decision aid to others that face the same treatment options as yourself?

- Yes
- Maybe
- No

Question 9
What did you like about the decision aid and information website?

Question 10
What suggestions do you have to improve this decision aid and website?

Appendix 14: Patient Knowledge Questionnaire

Please answer the following questions related to content found on this website.

Please enter the Study Participant Number that the Research Assistant has assigned to you in the space below: Note: This number is random and not linked to your personal information. All your answers will remain confidential.

Question 1

The following treatment options available to me for my current diagnosis of advanced pancreatic cancer are (select all that apply):

Radiation therapy Best supportive Care alone Chemotherapy Surgical resection of tumour None of the above I don't know

Question 2

Chemotherapy can cure my cancer

True False Unsure

Question 3

Chemotherapy can help treat symptoms caused by my cancer such as pain or fatigue

True False Unsure

Question 4

Chemotherapy can be associated with which of the following side effects (select all that apply):

Hair Loss Jaundice (yellowing of the skin) Vomiting/diarrhea Pain

Risk of infection

I don't know

Question 5

My cancer can continue to grow even if I am treated with chemotherapy

True False Unsure

Question 6

My chances of surviving longer are greater if I chose to be treated with Gemcitabine instead of FOLFIRINOX chemotherapy.

True False Unsure

Question 7

FOLFIRINOX is associated with more side effects than gemcitabine

True False Unsure

Question 8

I can stop my treatment at any time

True False Unsure

Question 9

On FOLFIRINOX, I will be treated at the hospital for: (selecton one that applies)

About 30 minutes x once a week About 2 hours x once a week About 5 hours every second week About 8 hours every second week Unsure

Question 10

If I take gemcitabine, I must wear a chemotherapy pump (5FU infusion pump) for 48 hours after every treatment visit:

True False