TOPIC: What is the comparative effectiveness of treatments for pancreatic ductal adenocarcinoma (PDAC) and its subtypes?

Methods

- We searched PUBMED and ClinicalTrials.gov for published and ongoing RCTs and Systematic Reviews of treatments for PDAC. The focus of this topic brief was on treatment and not screening or early detection strategies. However, since early detection of PDAC may impact treatment-related decision making and clinical outcomes, we reviewed ClinicalTrials.gov for ongoing screening studies, and we incorporated some suggestions for future research in our conclusions.
- Our team comprised an expert in comparative effectiveness research (Gillian Sanders Schmidler PhD), a family physician and epidemiologist (Remy Coeytaux MD, PhD), and a medical oncologist with expertise in pancreatic cancer (James Abbruzzese MD). Dr. Abruzzese is the Chief of the Duke Division of Medical Oncology and serves as the Associate Director for Clinical Research and Training for the Duke Cancer Institute (DCI). He serves as the Chair of the NCI Pancreatic Ductal Adenocarcinoma Progress Working Group. In that capacity, he convened a group of experts in the area of PDAC who presented a Report to the Director of the National Cancer Institute entitled, "Pancreatic Canter: Scanning the Horizon for Focused Interventions" in March, 2013.

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION[1-4] • The pancreas is an organ located near the stomach. The pancreas has both exocrine tissues that produce and release digestive enzymes into ducts that lead to the intestines and endocrine tissues that produce and release hormones such as insulin into the bloodstream. • More than 95% of malignant neoplasms of the pancreas arise from the exocrine tissues. • The term pancreatic ductal adenocarcinoma (PDAC) is generally used to refer to the approximately 85% of exocrine pancreatic cancers that are related to the pancreatic ductal cells and their stem cells. For the purpose of this topic brief, we focus primarily on PDAC. Below, when we use the term "pancreatic cancer" rather than PDAC we are referring to exocrine pancreatic neoplasms, which may include along with PDAC the several different types of cancers that comprise non-PDAC exocrine pancreatic cancers. • An AHRQ systematic review published in 2015[5] concluded that ultrasound, CT, MRI, cholangiopancreatography, and biomarkers are not reliable or feasible as screening tool for the general population. However, these tests are in common use despite weak and inconclusive evidence in support of their efficacy for screening purposes. • Currently, there are few effective treatment options for PDAC.
Relevance to patient-centered outcomes	SYMPTOMS • The most common presenting symptoms in patients with PDAC are abdominal or back pain, weight loss, anorexia, nausea, and diarrhea. Treatments for other causes of these symptoms tend not to be very effective when these symptoms occur in patients with PDAC. • Pain and weight loss are generally associated with stage of disease and subsequently worse survival in patients with PDAC. OUTCOMES[6] • PDAC is typically associated with debilitating symptoms, as listed above, followed by death within months or years of diagnosis, in part because most patients are diagnosed at a relatively late stage in the disease process, in part because pancreatic cancer has a tendency to metastasize quickly, and in part because treatments are not very effective. • PDAC has one of the highest case fatality rates of any malignancy. • The percentage of patients diagnosed with pancreatic cancer who lived 5 or more

	years after diagnosis in the United States from 2006-2012 was 7.7%.
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE (NEW CASES)[2-4] • There will be about 53,000 new cases of pancreatic cancer in the United States in 2016. This corresponds to a rate of approximately 12 new cases per year per 100,000 people. • Approximately 1.5% of men and women will be diagnosed with pancreatic cancer at some point during their lifetime, based on 2010-2012 data. • Rates for new pancreatic cancer cases have been rising on average 0.6% each year over the past 10 years. PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION) • In 2013, there were an estimated 49,620 people living with pancreatic cancer in the United States. • Pancreatic cancer is more common with increasing age, with a slightly higher prevalence in men than women, and among Blacks relative to other races. • There is an increased risk of PDAC in patients with obesity, diabetes mellitus (especially pancreogenic or type 3c diabetes which is caused by conditions that lead to damage of the pancreas), family history of PDAC, or presence of DNA repair defects such as PALB2, ATM, and most commonly BRCA1/2
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE[7] • All of the most common symptoms associated with PDAC (pain, weight loss, anorexia, nausea, etc.) have a profound impact on patient quality of life. • Most of the treatment options for PDAC have a negative impact on quality of life due to side effects such as fatigue, gastrointestinal symptoms, and hair loss, as well as high patient out-of-pocket costs. • Palliative surgeries intended to relieve symptoms and improve quality of life include: o surgical biliary bypass; o endoscopic stent placement; and o gastric bypass. • These are relatively invasive and costly interventions that introduce additional risk. • There is sparse evidence about the comparative effectiveness of these palliative surgeries. • Once patients are diagnosed with pancreatic cancer, they are generally no longer able to work. MORTALITY[2-4] • Although pancreatic cancer represents only 3% of all new cancer cases, it is the third leading cause of cancer death in the United States, after lung and colon cancer. More people are expected to die from pancreatic cancer than from breast cancer in the United States in 2016. • PDAC may become the second leading cause of cancer death by 2030. • The mortality rate of pancreatic cancer has increased an average of 0.4% annually from 2002-2011.[8]
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• A study published in 2012 estimated the mean total medical costs associated with pancreatic cancer among Medicare beneficiaries to be $65,500 per patient.[9] • Given the costs of PDAC, along with its impact on mortality, quality of life, and other important parameters, research on existing, emerging, and as-yet undiscovered PDAC treatment should be considered a high priority. • PDAC incidence has been increasing over the past 10 years, with no discernable improvement in prognosis over the same time period. This, combined with projections of PDAC becoming the second most common cause of cancer-related deaths, suggests that development of new screening and treatment approaches – and then studies which evaluate the comparative safety and effectiveness of such approaches

	should be given high priority.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	SCREENING/EARLY DIAGNOSIS[1-6,10] • There are currently no reliable or feasible tests for early pancreatic cancer detection. • There is no consensus regarding which individuals or populations should be screened for PDAC, or which molecular or imaging technologies to use for screening purposes. • In 2004, the US Preventative Services Task Force (USPSTF) did not recommend screening for PDAC in the general population.[10] The USPSTF, however, did not review literature for high-risk individuals, and there is a paucity of published evidence on this topic. • In 2012, the International Cancer of the Pancreas Screening (CAPS) Consortium recommended screening of patients with increased risk of familial pancreatic cancer.[11] • A recent AHRQ systematic review of imaging tests for the diagnosis and staging of PDAC found that the 6 included studies provide no evidence for conclusions about which imaging modalities are best for screening asymptomatic high-risk individuals (defined as having two or more first-degree relatives with pancreatic cancer or carrying specific genetic risk factors such as Peutz-Jeghers syndrome or carriers of BRCA2, PALB2, p16 gene mutations) for pancreatic cancer screening.[5] More studies within these high-risk individuals which evaluate similar screening strategies, populations, and outcomes of interest are needed. TREATMENT[1-4,6,12-21] • Most treatment options fall into one of the following categories: o Surgery o Radiation therapy o Chemotherapy o Chemoradiation therapy o Targeted therapy (e.g., tyrosine kinase inhibitors such as erlotinib) • There are also investigational approaches, including biologic therapy, stromal disruption (targeting the extracellular and cellular tissue framework that surrounds and interacts with cancer cells) immunotherapy; and novel targeted therapies. Most of these approaches are in Phase I/II trials currently. There is a trial of a stromal disrupting therapy (pegylated hyaluronidase) that will be heading in to Phase III trials soon (NCT02715804). Treatment broadly varies by stage, and for earlier stage cancers combined modality treatment is generally used: o Potentially resectable cancers – surgery and chemotherapy/chemoradiation o Locally advanced cancers – chemotherapy and chemoradiation o Metastatic – chemotherapy • There is good quality RCT evidence that provides guidance for management of patients with metastatic pancreatic cancer[22,23] and patients with locally advanced (unresectable) pancreatic cancer,[24] but survival is poor even with guidance-informed care. CER could help determine the best regimen to manage patients with metastatic pancreatic cancer (FLOFIRINOX vs gemcitabine/Nab-paclitaxel). • There are no randomized trials that address the questions of (1) pre-operative vs postoperative chemotherapy or chemoradiation for patients with resectable pancreatic cancer and (2) the optimal management of patients with borderline resectable pancreatic cancer (i.e., whether outcomes are better with standard adjuvant therapy following surgical resection vs. neo-adjuvant therapy followed by surgery).[25] • Surgery is the only curative therapy for PDAC, but it produces long-term, disease-free survival in only 3-4% of all individuals presenting with this disease, thereby suggesting that even therapy that is considered curative is associated with a low survival rate.

	○ Although surgery is the modality that is necessary for cure, almost all patients will relapse at some point following surgery. Given the low mortality of surgery the pendulum has shifted strongly away from questions regarding the value of surgery to those that address how additional therapeutic modalities can be added to surgery to generate more cures. The explanation for the poor outcomes includes late diagnosis and aggressive cancer biology whereby most patients (even with small pancreas primaries) probably already have micrometastatic disease. • The following drugs have received FDA approval for pancreatic cancer: erlotinib, , fluorouracil, gemcitabine, irinotecan hydrochloride liposome, mitomycin C, paclitaxel albumin-stabilized nanoparticle formulation.[26] ○ Generally, the single agents have only modest activity as judged by tumor regression; the best results are with combinations of 5FU/Irinotecan/Oxaliplatin or Gemcitabine/Nab-paclitaxel and with these agents the median improvement in overall survival is measured at 2-3 months. • A recently published integrated genomic analysis of PDCAs identified 32 recurrently mutated genes that aggregate into 10 pathways: KRAS; TGF-beta; WNT; NOTCH; ROBO/SLIT signaling; G1/S transition; SWI-SNF; chromatin modification, DNA repair; and RNA processing.[1] These new biological insights, coupled with an increased appreciation of the role of the immune system in cancer development and progression, inform the development of new classes of therapeutics that specifically target mechanisms through which PDAC tumors evade immune destruction. • Dissecting the tumor/stromal biology is a very active area of investigation. This includes understanding tumor stromal signaling, the role of specific stromal cells, infiltrating myeloid derived suppressor cells and even the extracellular matrix. Each of these areas of research (and others) provides new opportunities for novel therapeutic development. • The frequency of thromboembolic events in pancreatic cancer is very high. The tumor cells produce pro-thrombotic proteins (like tissue factor) that inappropriately stimulate the clotting mechanism. The results of a good-quality RCT of low molecular weight heparin (LMWH) as an adjunct to chemotherapy demonstrated a reduction in the frequency of deep vein thrombosis and pulmonary emboli in patients with pancreatic cancer was published in 2015. However, despite this, many oncologists are not prophylactically treating their patients with LMWH at this time,[27] possibly because of the recency of this new information, or possibly for other reasons including inadequate dissemination of findings or a low priority placed on this outcome by clinicians. • Current RCTs and systematic reviews (described below and in Tables 1 and 2) highlight the paucity of CER evidence of effective treatment strategies.
What could new research contribute to achieving better patient-centered outcomes?	• New research on the following could contribute to achieving better patient-centered outcomes in patients with pancreatic cancer by filling current knowledge gaps identified by clinical experts:[25] ○ Comparing approaches to improving/stabilizing nutrition/weight. ○ Comparing effectiveness of pain management approaches, e.g., value of celiac block vs. opioid therapy. ○ Comparing sequences of therapies, e.g., neo-adjuvant therapy vs. adjuvant therapy for patients with resectable cancer.
Have recent innovations made research on this topic especially compelling?	RECENT INNOVATIONS:[1,8] • Recently published expression analysis of 456 PDACs defined 4 subtypes: (1) squamous; (2) pancreatic progenitor; (3) immunogenic; and (4) aberrantly differentiated endocrine exocrine (ADEX). This recent understanding of the molecular evolution of pancreatic cancer subtypes provides potential new opportunities for therapeutic intervention. • The translation of these four pancreatic subtypes into clinically actionable information

	is currently hampered. One of the first issues will be to develop techniques that allow pathologists to efficiently classify cancers into the tumor subtypes without having to resort to very sophisticated bioinformatic methods. From there additional research is needed to identify therapeutic options that may be specific to one subgroup vs another. • There have been recent innovations in the understanding of the biology of PDAC and its various subtypes. For example: o Recent molecular descriptions of pancreatic cancer and pancreatic cancer subsets that may inform treatment decisions; o Better understanding of the importance of the pancreatic cancer stroma and development of organoid cultures that may facilitate development of stromal disruption treatment strategies and immunotherapy; o Initiatives around targeting mutations of the KRAS gene (which codes for protein that helps to regulate cell division) that may lead to new treatment strategies; o Development of genetically engineered mouse models of pancreatic cancer that may expedite the development and testing of new interventions.
How widely does care now vary?	VARIABILITY IN CARE • Evidence suggests that patient outcomes may be better at hospitals with multidisciplinary teams caring for patients with pancreatic cancer relative to smaller hospitals with individual surgeons and limited access to highly integrated, multidisciplinary teams.[28] • A study published in 2009 reported that the following indicators of quality of care for pancreatic cancer patients varied across hospitals: structural factors; clinical processes of care; treatment appropriateness; efficiency; and outcomes.[29]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS • Within PubMed (2011-present), we identified 12 relevant RCTs that evaluated treatment strategies for pancreatic cancer (Table 1)[30-41] and 10 systematic reviews (Table 2)[12-21] that reported on treatment strategies. • Study interventions included: gemcitabine; mycobacterium obuense, nanoliposomal irinotecan; fluorouracil and folinic acid; masitinib, adjuvant intra-arterial chemotherapy; surgery; ethanol celiac plexus neurolysis (ECPN); sunitinib; sequential GV1001 chemoimmunotherapy; CO-101 (a lipid-drug conjugate of gemcitabine); and induction chemoradiation vs. induction gemcitabine. • The available RCTs (Table 1) highlight both the lack of effectiveness of many studied treatments and for those treatments demonstrating benefit, the need for confirmatory studies of these findings through larger high-quality CERs which assess a broader area of important patient-centered outcomes. • The systematic reviews (Table 2) synthesized evidence about a variety of treatments in specific subgroups of interest but all emphasized the scarcity of data from large multi-center randomized clinical trials and the need for additional CER. ONGOING TRIALS • A review of treatment-related trials registered in ClinicalTrials.gov during the period 2011 to the present identified 71 trials that evaluated 1 or more interventions for pancreatic cancer (primarily PDAC). • During the same period, 7 studies registered in ClinicalTrials.gov are currently recruiting and evaluating screening strategies for pancreatic cancer. Screening strategies studied include pancreatic cancer screening pathways, ultrasound (3 studies), MRI (3 studies), and evaluation of pancreatic juice for early cancer markers. All studies target patients at high-risk for pancreatic cancer rather than from the general population. • Of the 71 treatment trials, 55 were identified by the study investigators as Phase 1 or 2 trials. Three were identified as Phase 3 RCTs o The study drugs and target sample size (N) of these 3 Phase 3 RCTs, all of

	which are ongoing, are: mFolfirinox vs. adjuvant therapy (N=490) [NCT01526135]; PEGylated Recombinant Human Hyaluronidase vs. placebo (N=420) [NCT02715804]; and Momelotinib vs. placebo (N=25) [NCT02101021]. o Primary outcomes within all trials are primarily survival rates and incidence and nature of adverse events. • Other than a single published (negative) RCT[35] (evaluating the use of ethanol celiac plexus neurolysis in patients undergoing pancreatic and periampullary adenocarcinoma resection) that identified pain as a primary outcome, none of the published or ongoing trials we identified appear to have symptom reduction or health-related quality of life as their primary or secondary outcomes. • Note that the Pancreatic Cancer Action Network (https://www.pancan.org/research/precision-promise/) is sponsoring Precision Promise, which is a large-scale precision medicine trial for patients with pancreatic cancer. The trial will start enrolling in Spring 2017 and 12 clinical trial consortium sites are involved. The goal of Precision Promise is to double pancreatic cancer survival by 2020. This initiative will investigate multiple treatment options under one clinical trial design. DNA damage repair defects, stromal disruption, and immunotherapy are the first treatment strategies to be evaluated. Future sub-studies may evaluate newly discovered biomarkers and treatment approaches.
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING PERTAINING TO THE TREATMENT OF PDAC The following uncertainties in clinical decision making were identified (and seen as similar importance) by our team's clinical expert: • Optimal front line chemotherapy for specific subgroups of patients with PDAC. • Management of weight loss and other symptoms associated with PDAC. • Optimal nutrition for patients with PDAC. • Optimal management of patients with resectable or borderline resectable PDAC.[42] • Role of screening in early detection; whom to screen; how to screen. • Role of prophylactic anti-thrombotic therapy. LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • Given the limited effectiveness on survival or quality-of-life outcomes of available treatments, appropriately designed RCTs of new and emerging therapies are needed to reduce these uncertainties. Currently, however, there may not be sufficient evidence from individual trials to support CER of existing treatments.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • Current treatment options for PDAC are limited in both the number of options and their effectiveness, so clinicians, patients, and policy makers are likely to be willing to implement new findings with proven effectiveness into practice. • Given the limited effectiveness of current treatments, even modest improvements in survival, symptomatic, and/or quality-of-life outcomes resulting from new research would likely be noticed and welcomed by patients and healthcare providers. BARRIERS • There may be relatively few barriers that would negatively affect the implementation of new findings from CER research that provided new information about treatment, diagnostic, or symptom-management options. Possible barriers include cost and/or accessibility of new treatment options, or possible need for training of healthcare providers for surgical or technical approaches.
How likely is it that the results of new research on this topic would	EVIDENCE OF BENEFIT • Given the poor survival and large quality of life impact of pancreatic cancer, findings would be likely to be implemented widely if there is evidence for better patient-centered outcomes, including health-related quality of life, symptom management

be implemented in practice right away?	(e.g., weight loss, nausea, fatigue, pain, etc.), and functional status. EVIDENCE OF NO BENEFIT OR HARM • Given the paucity of definitive evidence for either harms or effectiveness of various treatment strategies, new information that demonstrates the potential for harm would likely be readily incorporated in practice. If CER demonstrates no evidence of benefit, practice would not change.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	• There is currently active research on PDAC; given the limited success of available therapies, it is likely that new information about existing or new treatment options for PDAC would remain relevant for many years.
Conclusions	
	• Pancreatic cancer is a deadly disease for which treatment options are limited in their number and effectiveness. • There is ongoing, productive research that is contributing to the understanding of the biology and pathophysiology of various PDAC subtypes. • Recent evidence suggests potential benefit from screening high-risk populations, but currently there is little evidence to support early detection strategies for the general population. • There are many uncertainties in clinical decision making, including optimal front line therapies for different PDAC subtypes clinical presentation; effective symptomatic management; optimal nutrition; the role of prophylactic anti-thrombotic therapy; and the role of screening in early detection. • There is a paucity of good-quality RCTs that evaluate the effectiveness of emerging therapeutic strategies on survival, or that evaluate the effectiveness of therapeutic strategies for symptoms of pancreatic cancer and other patient-centered outcomes. • In the absence of high-quality RCTs evaluating emerging therapeutic strategies, opportunities for comparing known effective treatments may be limited. • However, given existing treatment options, CER could be helpful to sort out the optimal approach to patients with resectable pancreatic cancer and the optimal strategies for palliation of cancer-related symptoms such as pain, weight loss/cachexia, fatigue. • Given the limited effectiveness of available treatments and screening strategies, there is a high likelihood that appropriately designed CER studies which targeted identified uncertainties and demonstrated safe and effective strategies would be well received and impact patient care and clinical practice • Significant improvements in clinical outcomes associated with PDAC may require a two-pronged approach that includes research on both early detection and treatment strategies.

Table 1. Overview of Recently Published RCTs in Treatment of PDAC

Author, year	N	Study Interventions	Outcomes Assessed	Conclusions
Dalgleish, 2016[30]	110	Arm 1: Mycobacterium obuense with gemcitabine Arm 2: gemcitabine alone	Overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) were collected.	IMM-101 with GEM was as safe and well tolerated as GEM alone, and there was a suggestion of a beneficial effect on survival in patients with metastatic disease. This warrants further evaluation in an adequately powered confirmatory study.
Uesaka, 2016[31]	385	Arm 1: gemcitabine Arm 2: Adjuvant chemotherapy of S-1	OS, adverse events (AE)	Adjuvant chemotherapy with S-1 can be a new standard care for resected pancreatic cancer in Japanese patients. These results should be assessed in non-Asian patients.
Wang-Gillam, 2016[32]	417	Arm 1: nanoliposomal irinotecan monotherapy Arm 2: fluorouracil and folinic acid Arm 3: nanoliposomal irinotecan	OS, AE	Nanoliposomal irinotecan in combination with fluorouracil and folinic acid extends survival with a manageable safety profile in patients with metastatic pancreatic ductal adenocarcinoma who previously received gemcitabine-based therapy. This agent represents a new treatment option for this population.
Deplanque, 2015[33]	353	Arm 1: masitinib plus gemcitabine Arm 2: placebo plus gemcitabine	OS, AE	The present data warrant initiation of a confirmatory study that may support the use of masitinib plus gemcitabine for treatment of PDAC patients with overexpression of ACOX1 or baseline pain (VAS > 20mm). Masitinib's effect in these subgroups is also supported by biological plausibility and evidence of internal clinical validation.
Erdmann, 2015[34]	120	Arm 1: adjuvant intra-arterial chemotherapy Arm 2: surgery alone	Long-term survival, metastases,	This long-term analysis shows that median and long-term survival were improved after IAC/RT in patients with NPPC, probably because of the effective and sustained reduction of liver metastases. The present results illustrate that NPPC requires an adjuvant approach distinct from that in pancreatic cancer and indicate that further investigation of this issue is warranted.
Lavu, 2015[35]	485	Arm 1: Ethanol celiac plexus neurolysis (ECPN) Arm 2: saline placebo	short- and long-term pain and secondary endpoints included postoperative morbidity, quality of life, and overall survival.	In this study, a significant reduction in pain was demonstrated after surgical resection of pancreatic and periampullary adenocarcinoma. However, the addition of ECPN did not synergize to result in a further reduction in pain, and in fact, its effect may have been masked by surgical resection. Given this, the use of ECPN is not recommended to mitigate cancer-related pain in resectable PPA

				patients.
Bergmann, 2015[36]	106	Arm 1: gemcitabine (GEM) Arm 2: gemcitabine plus sunitinib (SUNGEM)	progression free survival (PFS), secondary end-points were overall survival (OS), toxicity and overall response rate (ORR).	The combination SUNGEM was not sufficient superior in locally advanced or metastatic PDAC compared to GEM alone in regard to efficacy but was associated with more toxicity.
Middleton, 2014[37]	1062	Arm 1: chemotherapy alone Arm 2: chemotherapy with sequential GV1001 (sequential chemoimmunotherapy) Arm 3: chemotherapy with concurrent GV1001 (concurrent chemoimmunotherapy)	OS, AE	Adding GV1001 vaccination to chemotherapy did not improve overall survival. New strategies to enhance the immune response effect of telomerase vaccination during chemotherapy are required for clinical efficacy.
Sahora, 2014[38]	30	Arm 1: gemcitabine Arm 2: bevacizumab + gemcitabine	OS	In general, adding bevacizumab to neoadjuvant gemcitabine does not improve outcomes for patients with locally advanced pancreatic cancer. However, in individual cases, surgery is consequently possible and prolonged survival may be observed.
Poplin, 2013[39]	367	Arm 1: CO-101, a lipid-drug conjugate of gemcitabine Arm 2: gemcitabine	OS	CO-101 is not superior to gemcitabine in patients with mPDAC and low tumor hENT1. Metastasis hENT1 expression did not predict gemcitabine outcome.
Lohr, 2012[40]	212	Arm 1: GEM Arm 2: GEM +ET (Paclitaxel embedded in cationic liposomes (EndoTAG-1; ET)	OS	Treatment of advanced PDAC with GEM + ET was generally well tolerated. GEM + ET showed beneficial survival and efficacy. A randomized phase III trial should confirm this positive trend.
Barhoumi, 2011[41]	119	Arm 1: induction chemoradiation + maintenance GEM Arm 2: induction gemcitabine + maintenance GEM	OS	This intensive induction schedule of chemoradiation was more toxic and less effective than gemcitabine alone.

Table 2. Overview of Recently Published Systematic Reviews in the Treatment of PDAC

Author, Year	Objective of Review	Search Dates	N Included Studies	Main Findings
Antoniou, 2016[12]	To summarize the current state of knowledge regarding the potential effectiveness of liver metastasectomy in the setting of PDAC	1990-2015	8	Results suggest that hepatic metastasectomy for PDAC is a safe procedure, with a potential survival benefit for carefully selected patients, particularly those with metachronous metastases. Nonetheless, small sample sizes and inconsistent use of appropriate controls preclude generalization of these findings. Multi-institutional prospective studies are required to fully delineate the potential therapeutic utility and operative indications of liver metastasectomy in the setting of modern interdisciplinary management of PDAC.
Riviere, 2016[13]	To assess the benefits and harms of laparoscopic distal pancreatectomy versus open distal pancreatectomy for people undergoing distal pancreatectomy for pancreatic ductal adenocarcinoma of the body or tail of the pancreas, or both.	Cut-off: June 2015	12	Randomized controlled trials are needed to compare laparoscopic distal pancreatectomy versus open distal pancreatectomy with at least two to three years of follow-up. Such studies should include patient-oriented outcomes such as short-term mortality and long-term mortality (at least two to three years); health-related quality of life; complications and the sequelae of complications; resection margins; measures of earlier postoperative recovery such as length of hospital stay, time to return to normal activity and time to return to work (in those who are employed); and recurrence of cancer.
Giovinazzo, 2016[14]	To compare the results of pancreatic resection with portal-superior mesenteric vein (PV-SMV) resection for suspected infiltration with the results of surgery without PV-SMV resection.	Time of inception to 2013	27	This meta-analysis showed increased postoperative mortality, higher rates of non-radical surgery and worse survival after pancreatic resection with PV-SMV resection. This may be related to more advanced disease in this group.
Nagrial, 2015[15]	To systematically review and synthesize all prospective data available for the second-line treatment of advanced PDAC.	Inception through Jan 24, 2014	24 first-line studies and 71 second-line studies	The reported use of second-line systemic therapy in pancreatic adenocarcinoma studies has increased over time and correlates with survival, but is not reported in the majority of published studies. Although a large number of therapies have been explored in this setting, no particular therapy can be universally recommended. Studies of targeted therapies have been primarily performed in unselected populations and outcomes have been disappointing. Future studies need to include significant translational components so that predictive biomarkers can be assessed.
Petrelli, 2015[16]	To evaluate progression-free survival as a potential surrogate endpoint for overall survival (OS) in advanced pancreatic cancer in	2002-2013	30	Because of the robust correlation with OS and the potential influence of post progression survival caused by the second line therapies, it may be justified to consider progression free survival as a surrogate endpoint in trials evaluating new

	trials comparing poly-chemotherapy to gemcitabine alone.			cytotoxic agents when gemcitabine is the control arm.
Koh, 2015[17]	To determine the clinical importance of the histologic subtypes of noninvasive and invasive intraductal papillary mucinous neoplasms (IPMNs) on disease characteristics and overall survival.	Jan 1, 1999, to Sep 14, 2013	14	The prognosis of IPMN depends on its pathologic subtype. Subtype identification should be considered an essential component in future guidelines for the management of IPMN.
Ricci, 2015[18]	To review the safety and effectiveness of: laparoscopic distal pancreatectomy for pancreatic ductal adenocarcinoma.	Cut-off: 2014	5	The treatment of PDAC seems to be safe and efficacious. However, additional prospective, randomized, multicentric trials are needed to correctly evaluate the laparoscopic approach in PDAC.
Ozola, 2015[19]	To assess the prevalence and consequences of cachexia and sarcopenia on survival in patients with pancreatic ductal adenocarcinoma.	Cut-off: Dec 2013	10	Impact of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma is currently understudied in the available literature. Definitive association between cachexia and survival cannot be drawn from available studies, although weight loss and sarcopenic obesity might be considered as poor prognostic factors. Further prospective trials utilizing the consensus definition of cachexia and including other confounding factors are needed to investigate the impact of cachexia and sarcopenia on survival in pancreatic adenocarcinoma.
Koh, 2014[20]	To summarize the current literature comparing the surgical outcomes of invasive intraductal papillary mucinous neoplasms (IPMN(INV)) and conventional pancreatic ductal adenocarcinomas (PDAC) in order to determine the differences in disease characteristics and prognosis.	Cut-off: Jul 30, 2013	12	IPMN(INV) were significantly more likely to present at an earlier stage and were less likely to demonstrate nodal involvement, perineural invasion and vascular invasion. When controlled for stage, IPMN(INV) had an improved OS when compared with PDAC in the early stages.
Fegrachi, 2014[21]	To evaluate the safety and effectiveness of radiofrequency ablation in patients with unresectable locally advanced pancreatic cancer	Cut-off: Jan 1, 2012	5	Radiofrequency ablation seems to be feasible and safe when it is used with the correct temperature and at an appropriate distance from vital structures. It appears to have a positive impact on survival. Multicenter randomized trials are necessary to determine the true effect size of RFA and to minimize the impacts of selection and publication biases.

REFERENCES:

1. Bailey P, Chang DK, Nones K, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature 2016;531(7592):47-52. PMID: 26909576.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7-30. PMID: 26742998.
3. UpToDate® [search portal: www.uptodate.com]. Search results for “pancreatic cancer.” Search conducted September 23, 2016.
4. National Cancer Institute. SEER Stat Fact Sheets: Pancreas Cancer [web page]. http://seer.cancer.gov/statfacts/html/pancreas.html. Accessed September 23, 2016.
5. Treadwell J, Mitchell M, Eatmon K, et al. Comparative Effectiveness Review. Imaging Tests for the Diagnosis and Staging of Pancreatic Adenocarcinoma. 2014. In: Quality AfHRa, ed. Rockville, MD: Agency for Healthcare Research and Quality. Link: https://www.effectivehealthcare.ahrq.gov/ehc/products/513/1972/cancer-pancreas-report-140929.pdf.
6. National Cancer Institute, Pancreatic Cancer Working Group and Clinical Trials and Translational Research Advisory Committee. Pancreatic Cancer: Scanning the Horizon for Focused Interventions. March 13, 2013. http://deainfo.nci.nih.gov/advisory/ctac/archive/0313/PCwgReport.pdf. Accessed September 23, 2016.
7. American Society of Clinical Oncology. Pancreatic Cancer [web page]. http://www.cancer.net/cancer-types/pancreatic-cancer/treatment-options. Assessed September 23, 2016.
8. National Cancer Institute. A Snapshot of Pancreatic Cancer [web page]. www.cancer.gov/research/progress/snapshots/pancreatic. Accessed September 23, 2016.
9. O'Neill CB, Atoria CL, O'Reilly EM, et al. Costs and trends in pancreatic cancer treatment. Cancer 2012;118(20):5132-9. PMID: 22415469.
10. U.S. Preventive Services Task Force. Screening for pancreatic cancer: recommendation statement. Rockville, MD: Agency for Healthcare Research and Quality; 2004 Feb. 3.
11. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013;62(3):339-47. PMID: 23135763.
12. Antoniou E, Margonis GA, Sasaki K, et al. Is resection of pancreatic adenocarcinoma with synchronous hepatic metastasis justified? A review of current literature. ANZ J Surg 2016. PMID: 27580713.
13. Riviere D, Gurusamy KS, Kooby DA, et al. Laparoscopic versus open distal pancreatectomy for pancreatic cancer. Cochrane Database Syst Rev 2016;4:Cd011391. PMID: 27043078.
14. Giovinazzo F, Turri G, Katz MH, et al. Meta-analysis of benefits of portal-superior mesenteric vein resection in pancreatic resection for ductal adenocarcinoma. Br J Surg 2016;103(3):179-91. PMID: 26663252.
15. Nagrial AM, Chin VT, Sjoquist KM, et al. Second-line treatment in inoperable pancreatic adenocarcinoma: A systematic review and synthesis of all clinical trials. Crit Rev Oncol Hematol 2015;96(3):483-97. PMID: 26481952.
16. Petrelli F, Coinu A, Borgonovo K, et al. Progression-free survival as surrogate endpoint in advanced pancreatic cancer: meta-analysis of 30 randomized first-line trials. Hepatobiliary Pancreat Dis Int 2015;14(2):124-31. PMID: 25865683.
17. Koh YX, Zheng HL, Chok AY, et al. Systematic review and meta-analysis of the spectrum and outcomes of different histologic subtypes of noninvasive and invasive intraductal papillary mucinous neoplasms. Surgery 2015;157(3):496-509. PMID: 25656693.

18. Ricci C, Casadei R, Taffurelli G, et al. Laparoscopic versus open distal pancreatectomy for ductal adenocarcinoma: a systematic review and meta-analysis. J Gastrointest Surg 2015;19(4):770-81. PMID: 25560180.

19. Ozola Zalite I, Zykus R, Francisco Gonzalez M, et al. Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: a systematic review. Pancreatology 2015;15(1):19-24. PMID: 25524484.

20. Koh YX, Chok AY, Zheng HL, et al. Systematic review and meta-analysis comparing the surgical outcomes of invasive intraductal papillary mucinous neoplasms and conventional pancreatic ductal adenocarcinoma. Ann Surg Oncol 2014;21(8):2782-800. PMID: 24687151.

21. Fegrachi S, Besselink MG, van Santvoort HC, et al. Radiofrequency ablation for unresectable locally advanced pancreatic cancer: a systematic review. HPB (Oxford) 2014;16(2):119-23. PMID: 23600801.

22. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817-25. PMID: 21561347.

23. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691-703. PMID: 24131140.

24. Hammel P, Huguet F, van Laethem JL, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. Jama 2016;315(17):1844-53. PMID: 27139057.

25. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med 2014;371(11):1039-49. PMID: 25207767.

26. National Cancer Institute. Drugs Approved for Pancreatic Cancer [web page]. www.cancer.gov/about-cancer/treatment/drugs/pancreatic. Accessed September 23, 2016.

27. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of Prophylactic Low-Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial. J Clin Oncol 2015;33(18):2028-34. PMID: 25987694.

28. Derogar M, Blomberg J, Sadr-Azodi O. Hospital teaching status and volume related to mortality after pancreatic cancer surgery in a national cohort. Br J Surg 2015;102(5):548-57; discussion 557. PMID: 25711855.

29. Bilimoria KY, Bentrem DJ, Lillemoe KD, et al. Assessment of pancreatic cancer care in the United States based on formally developed quality indicators. J Natl Cancer Inst 2009;101(12):848-59. PMID: 19509366.

30. Dalgleish AG, Stebbing J, Adamson DJ, et al. Randomised, open-label, phase II study of gemcitabine with and without IMM-101 for advanced pancreatic cancer. Br J Cancer 2016. PMID: 27599039.

31. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet 2016;388(10041):248-57. PMID: 27265347.

32. Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016;387(10018):545-57. PMID: 26615328.

33. Deplanque G, Demarchi M, Hebbar M, et al. A randomized, placebo-controlled phase III trial of masitinib plus gemcitabine in the treatment of advanced pancreatic cancer. Ann Oncol 2015;26(6):1194-200. PMID: 25858497.

34. Erdmann JI, Morak MJ, Duivenvoorden HJ, et al. Long-term survival after resection for non-pancreatic periampullary cancer followed by adjuvant intra-arterial chemotherapy and concomitant radiotherapy. HPB (Oxford) 2015;17(7):573-9. PMID: 25800041.

35. Lavu H, Lengel HB, Sell NM, et al. A prospective, randomized, double-blind, placebo controlled trial on the efficacy of ethanol celiac plexus neurolysis in patients with operable pancreatic and periampullary adenocarcinoma. J Am Coll Surg 2015;220(4):497-508. PMID: 25667135.

36. Bergmann L, Maute L, Heil G, et al. A prospective randomised phase-II trial with gemcitabine versus gemcitabine plus sunitinib in advanced pancreatic cancer: a study of the CESAR Central European Society for Anticancer Drug Research-EWIV. Eur J Cancer 2015;51(1):27-36. PMID: 25459392.

37. Middleton G, Silcocks P, Cox T, et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. Lancet Oncol 2014;15(8):829-40. PMID: 24954781.

38. Sahora K, Schindl M, Kuehrer I, et al. A phase II trial of two durations of Bevacizumab added to neoadjuvant gemcitabine for borderline and locally advanced pancreatic cancer. Anticancer Res 2014;34(5):2377-84. PMID: 24778046.

39. Poplin E, Wasan H, Rolfe L, et al. Randomized, multicenter, phase II study of CO-101 versus gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma: including a prospective evaluation of the role of hENT1 in gemcitabine or CO-101 sensitivity. J Clin Oncol 2013;31(35):4453-61. PMID: 24220555.

40. Lohr JM, Haas SL, Bechstein WO, et al. Cationic liposomal paclitaxel plus gemcitabine or gemcitabine alone in patients with advanced pancreatic cancer: a randomized controlled phase II trial. Ann Oncol 2012;23(5):1214-22. PMID: 21896540.

41. Barhoumi M, Mornex F, Bonnetain F, et al. [Locally advanced unresectable pancreatic cancer: Induction chemoradiotherapy followed by maintenance gemcitabine versus gemcitabine alone: Definitive results of the 2000-2001 FFCD/SFRO phase III trial]. Cancer Radiother 2011;15(3):182-91. PMID: 21315644.

42. Hoffe S, Rao N, Shridhar R. Neoadjuvant vs adjuvant therapy for resectable pancreatic cancer: the evolving role of radiation. Semin Radiat Oncol 2014;24(2):113-25. PMID: 24635868.