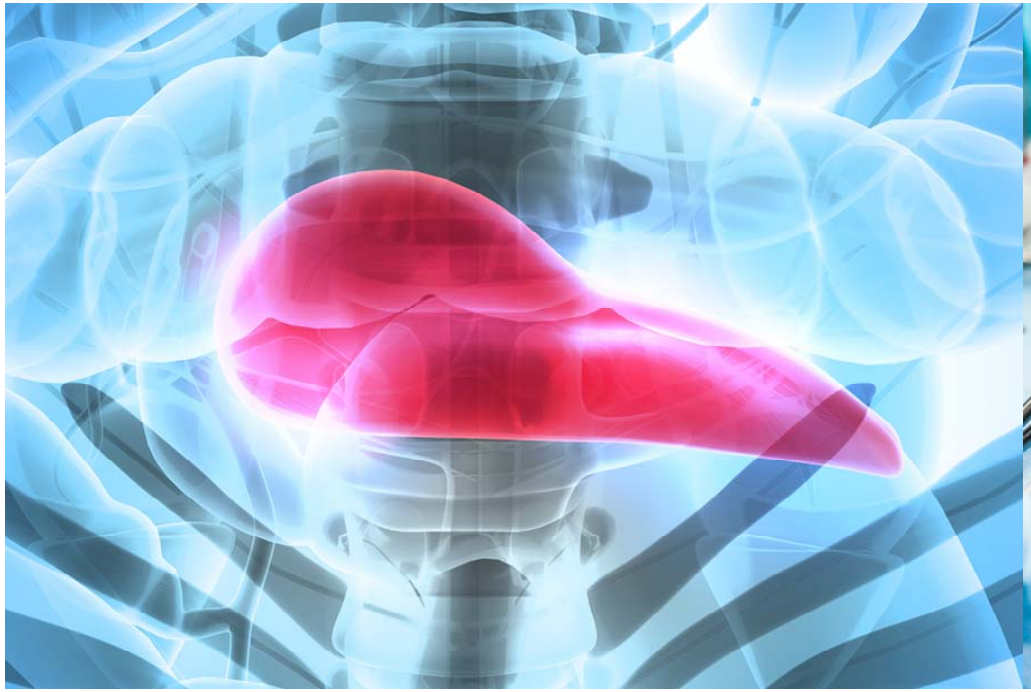
KCE REPORT 286

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

MANAGEMENT OF PANCREATIC CANCER PART 2: DIAGNOSIS



KCE REPORT 286
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

MANAGEMENT OF PANCREATIC CANCER PART 2: DIAGNOSIS

GENEVIÈVE VEEREMAN, MARC PEETERS, KURINCHI GURUSAMY, CHRISTIANA NAAKTGEBOREN, LOTTY HOOFT, NADIA HAJ MOHAMMAD, MAARTEN VAN LEEUWEN, ROB SCHOLTEN, HANS VAN BRABANDT

COLOPHON

Title:	Management of pancreatic cancer Part 2: Diagnosis
Authors:	Geneviève Veereman (KCE), Marc Peeters (UZA), Kurinchi Gurusamy (Dutch Cochrane Centre), Christiana Naaktgeboren (Dutch Cochrane Centre), Lotty Hooft (Dutch Cochrane Centre), Nadia Haj Mohammad (Dutch Cochrane Centre), Maarten Van Leeuwen (Dutch Cochrane Centre), Rob Scholten (Dutch Cochrane Centre), Hans Van Brabandt (KCE)
Guideline Development Group:	Marc Peeters (President of the GDG, UZA), Frederik Berrevoet (UGent), Ivan Borbath (Cliniques universitaires Saint-Luc), Donald Claeys (AZMMSJ), Joelle Collignon (UZ Leuven), Pieter Demetter (Hôpital Erasme), Karen Geboes (UGent), Karin Haustermans (UZ Leuven), Mina Komuta (Cliniques universitaires Saint-Luc), Philippe Malvaux (CHWAPI, Tournai), Els Monsaert (AZMMSJ), Hans Prenen (CHU Liège), Geert Roeyen (UZA), Bart Smet (AZ Delta), Sigrid Stroobants (UZA), Baki Topal (UZ Leuven), Eric Van Cutsem (UZ Leuven), Daniel Van Daele (CHU Liège), Daniel Van Gansbeke (Hôpital Erasme), Jean-Luc Van Laethem (Hôpital Erasme), Joseph Weerts (CHC Liège)
Scoping of the guideline:	Frederik Berrevoet (UGent), Alain Bols (BSMO), Nicolas Christian (BVRO – ABRO), An Claes (Kom op tegen Kanker), Wim Demey (BSMO), Joelle Collignon (UZ Leuven), Pieter Demetter (Hôpital Erasme), Lorraine Donnay (BVRO – ABRO), Karen Geboes (UGent), Bernard Geurde (BGES), Anne Hoorens (BVP-SBP), Catherine Hubert (BSHBPS – RBSS), Philippe Malvaux (CHWAPI, Tournai), Els Monsaert (AZMMSJ), Geert Roeyen (UZA), Raphael Rubay (BGES), Marc Simoens (VVGE), Bart Smet (AZ Delta), Baki Topal (UZ Leuven), Daniel Van Daele (CHU Liège), Nancy Van Damme (Stichting Kanker Register), Daniel Van Gansbeke (Hôpital Erasme), Jean-Luc Van Laethem (Hôpital Erasme), Joseph Weerts (CHC Liège), Dirk Ysebaert (BSSO)
Project Coordinator:	Sabine Stordeur (KCE)
Reviewers:	Anja Desomer (KCE), Raf Mertens (KCE), Joan Vlayen (KCE)
Stakeholders:	Alain Bols (BSMO), Nicolas Christian (BVRO-ABRO), An Claes (Kom op tegen Kanker), Wim Demey (BSMO), Lorraine Donnay (BVRO – ABRO), Bernard Geurde (BGES), Anne Hoorens (BVP – SBP), Catherine Hubert (BSHBPS – RBSS), Raphael Rubay (BGES), Marc Simoens (VVGE), Nancy Van Damme (Stichting KankerRegister), Didier Van der Steichel (Fondation Contre le Cancer), Dirk Ysebaert (BSSO)
External validators:	Marco Bruno (University Medical Center Rotterdam), Bas Groot Koerkamp (University Medical Center Rotterdam), Thomas Seufferlein (Universitätsklinikum Ulm)
Other reported interests:	Membership of a stakeholder group on which the results of this report could have an impact: Alain Bols (BSMO), Marco Bruno (ESDO), Wim Demey (BSMO), Els Monsaert (VVGE), Marc Simoens (VVGE), Didier Van der Steichel (General Director, Fondation contre le Cancer)

	Participation in scientific or experimental research as an initiator, principal investigator or researcher: Marco Bruno (several studies), Karen Geboes (many commercial studies related to metastatic pancreatic cancer), Karin Haustermans (Topgear, international study related to gastric cancer), Anne Hoorens (collaboration studies Baltimore, IPMN early genetics), Thomas Seufferlein (Clinical trial as PI for CELGENE) A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Marco Bruno (Via Boston Scientific, via Cook Medical), (Thomas Seufferlein (Research support by CELGENE) Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Marco Bruno (Via Boston – scientific, via Cook Medical), Thomas Seufferlein (Speakers fees and travel costs reimbursed by CELGENE and Shire) Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Geert Roeyen (Board member HPBS – RBSS), Dirk Ysebaert (Head of service hepatobiliary, transplantation and endocrine surgery UZA; vice-dean Faculty of Medicine, University of Antwerp), Didier Van der Steichel (Patient Information)
Layout:	Joyce Grijseels, Ine Verhulst

Disclaimer:	• **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** • **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** • **Finally, this report has been approved by common assent by the Executive Board.** • **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

Publication date:	2 February 2018 (2nd print, 1st print: 15 May 2017)
Domain:	Good Clinical Practice (GCP)
MeSH:	Pancreatic neoplasm, Practice Guideline
NLM Classification:	WI 810
Language:	English

Format: Adobe® PDF™ (A4)

Legal depot: D/2017/10.273/30

How to refer to this document? Veereman G, Peeters M, Gurusamy K, Naaktgeboren C, Hooft L, Haj Mohammad N, Van Leeuwen M, Scholten R, Van Brabandt H. Management of pancreatic cancer Part 2: Diagnosis. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2017. KCE Reports 286. D/2017/10.273/30.

This document is available on the website of the Belgian Health Care Knowledge Centre.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
CA19-9	Carbohydrate antigen 19-9
CEA	Carcino embryonal antigen
CI	Confidence interval
CT	Computed tomography
EUS	Endoscopic ultrasound
FN	False negative
FNA	Fine needle aspiration
FP	False positive
GDG	Guideline development group
IPMN	Intraductal papillary mucinous neoplasms
KCE	Belgian health care knowledge centre
mRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NCCN	National comprehensive cancer network
PCN	Pancreatic cystic neoplasms
PET	Positron emission tomography
PET-CT	Positron emission tomography - computed tomography
P.I.R.T.	Population - index test - reference test - target disorder
RQ	Research question
SR	Systematic review
SUV	Standardized uptake values
TN	Total negatives
TP	Total positives
US	Ultrasonography
yrs	Years

SCIENTIFIC REPORT

1 INTRODUCTION

This chapter addresses the research question (RQ) on diagnostic strategy. The RQ was translated into population - index test - reference test - target disorder (P.I.R.T.) as follows:

Table 1 – P.I.R.T.

What is the best diagnostic strategy in the following conditions? 1. Suspicion of resectable pancreatic cancer 2. Suspicion of borderline resectable pancreatic cancer 3. Suspicion of locally advanced pancreatic cancer	
P (patient)	1. Patients suspected of resectable pancreatic cancer 2. Patients suspected of borderline resectable cancer 3. Patients suspected of locally advanced pancreatic cancer
I (Intervention)	computed tomography (CT) magnetic resonance imaging (MRI) different technologies, magnetic resonance cholangiopancreatography (mRCP) endoscopic ultrasound (EUS) +/- fine needle aspiration (FNA) +/- cyst fluid analysis positron emission tomography (PET) scan tumour markers: carbohydrate antigen 19-9 (CA19.9) and carcino embryonal antigen (CEA) laparoscopy
R (Reference standard)	Histopathology and/or clinical follow-up and/or surgery
T (Target)	Diagnosis, assess resectability

The suspicion of pancreatic cancer is usually based on finding a pancreatic lesion during imaging of the upper abdomen for painless jaundice, for non-specific upper abdominal complaints or imaging for other reasons (e.g. ultrasound or CT of the upper abdomen). In the latter case, the pancreatic lesion is an incidental finding. Usually, CT will be the first, and often only, used imaging modality, on which further (diagnostic or therapeutic) management will be based. [1] In clinical practice, MRI, including MRCP, and EUS with or without FNA and with or without cyst fluid analysis, and biomarkers are often used to further assess the nature of the lesion.

In order to address the first diagnostic challenge in assessing the nature (benign vs. malignant) of the lesion, the following P.I.R.T. was used.

Table 2 – P.I.R.T. part 1

Patients	Intervention(s)	Comparator(s)	Outcomes
Adults ≥18 years of age with a focal lesion on pancreatic imaging	CT, MRI / MRCP PET(/CT) EUS with or without FNA with or without cyst fluid analysis Tumour markers: Ca19.9, CEA	Tests are compared with each other, either directly (head-to-head) or indirectly*	Diagnostic outcomes: sensitivity, specificity, predictive values for pancreatic or periampullary cancer vs no cancer (benign lesion) assessed by histopathology and/or clinical follow-up (and/or surgery).

Table 3 – P.I.R.T. part 2

Patients	Intervention(s)	Comparator(s)	Outcomes
Adult patients (≥18 years of age) with a focal pancreatic lesion on CT (or on another imaging technique) that is judged to be malignant (i.e. requires surgery)	CT; MRI, MRCP, PET(/CT) EUS with or without FNA laparoscopy as add-on test to a positive imaging result (usually CT)	Tests are compared with each other (replacement), either directly (head-to-head) or indirectly, or with no further testing	Diagnostic outcomes: sensitivity, specificity, predictive values for curative tumour resectability (according to the National Comprehensive Cancer Network (NCCN) criteria assessed by histopathology and/or clinical follow-up and/or surgery

Subsequently, when a focal pancreatic lesion is judged to be malignant and, therefore, considered for surgical resection, the next question is: is the lesion surgically resectable or not? A tumour is not resectable if it is locally advanced (precluding complete resection), and/or if there are distant metastases (e.g. in the lungs, liver, peritoneum). If the tumour is judged to be resectable, surgery will follow (usually without histopathological confirmation). Another outcome of diagnostic imaging may be that the tumour is borderline resectable (if one is not sure about its resectability) or not resectable.Therefore, the second part of the RQ was addressed as follows:

2 STUDY IDENTIFICATION AND SELECTION

The search for systematic reviews (SR) was limited by browsing the topics list of the Cochrane Upper Gastro Intestinal and Pancreatic Diseases Group (search date May 9, 2016). One SR[2] and two protocols for SRs,[3, 4] of which the completed reviews were both in the editorial process and subsequently published respectively by Tamburrino et al.[5] and Best et al.[6] were relevant to this RQ. It was decided to use these three reviews given their recent search dates. On 15 November 2016 the search of Allen 2016 was updated.[2] MEDLINE, Embase, CENTRAL and Cochrane Register of Diagnostic Test Accuracy Studies, and Science Citation Index were searched to identify studies regarding the diagnostic test accuracy of laparoscopy following CT for assessing the resectability with curative intent in patients with pancreatic or peri-ampullary cancer and published from May 1, 2016 onwards. In total, 1444 potentially relevant references were identified (seeFigure 2 in the Appendix). After deduplication, 875 references remained. Based on title and abstract 855 references were excluded. All of the remaining 20 references were excluded with reason (Table 4).

On November 15th, 2016 the search of Tamburrino was updated.[5] MEDLINE, Embase, Science Citation Index, and National Institute for Health Research - Health Technology Assessment were searched to identify studies regarding the diagnostic test accuracy of different imaging modalities following CT for assessing the resectability with curative intent in patients with pancreatic or peri-ampullary cancer and published from November 1, 2015 onwards. In total, 1533 potentially relevant references were identified (see Figure 3 in the Appendix). After deduplication, 1215 references remained. Based on title and abstract 1204 references were excluded. All of the remaining 11 references were excluded with reason (Table 5).

On December 5th, 2016 the search of Cao 2016 was updated.[7] MEDLINE and Embase were searched to identify studies regarding the diagnostic test accuracy of CA 19-9 for diagnosing malignancy in patients with pancreatic or peri-ampullary lesions published from March 1, 2016 onwards. Instead of using the exact search used by Cao, a wider search on all biomarkers was chosen so that it could also be used for the review on CEA. In total, 2371 potentially relevant references were identified (see Figure 4 in the Appendix) After deduplication, 1619 references remained. Based primarily on date, title and abstract 1609 references were excluded. Of the 10 remaining references, nine were excluded with reason (Table 6), leaving one study that could be added to the update: Gu 2016.[8]

On December 5th, 2016 the MEDLINE and Embase were searched to identify studies regarding the diagnostic test accuracy of CEA for diagnosing malignancy in patients with pancreatic or peri-ampullary lesions. In total, 2371 potentially relevant references were identified (Figure 5). After deduplication, 1619 references remained. Based on title and abstract 1571 references were excluded. Forty-five references were excluded with reason (Table 7), resulting in only three studies that could be used: Aljebreen 2007[9], Ni 2005[10] and Goh 2008.[11]

3 EVIDENCE DESCRIPTION

3.1 Imaging tests to diagnose malignant pancreatic lesions

A protocol for a Cochrane SR was found on the diagnostic accuracy of imaging tests for characterizing focal pancreatic lesions. The the authors of the corresponding manuscript agreed to share the final manuscript before publication.[4, 6] This study searched for studies on imaging tests published until July 2016. The authors identified 53 studies (with a total of 3118 patients) that evaluated the diagnostic accuracy of various index tests for different final diagnoses (including benign, precancerous and cancerous lesions). Imaging tests that were searched for were CT, MRI, PET, EUS, EUS elastography, and EUS-guided biopsy either alone or in combination with another test.

Not all studies in this review were relevant to the RQ at hand; only the studies that looked at the ability of various imaging modalities to differentiate between cancerous and benign lesions (11 studies, 533 patients) or between either precancerous (low grade dysplasia) or cancerous and benign lesions (7 studies, 204 patients) were relevant and summarized here.

3.1.1 Differentiating between cancerous and benign lesions

Of the 11 studies on differentiating between cancerous versus benign lesions there were two studies on EUS, two studies on EUS with FNA cytology (fine needle aspiration), three studies on PET, one study on PET (Standardised UIptake Value: SUV max >3.5), two studies on CT, and one study on MRI. The median pre-test probability of a malignant lesion in these studies was 70% (range 23 to 89%). The respective pooled (or single study) estimates (with 95% confidence interval (CI)) of sensitivity and specificity were 0.95 (0.84-0.99) and 0.53 (0.31-0.74) for EUS, 0.58 (0.37-0.77) and 1.0 (95% CI 0.87 to 1,.00) for EUS FNA, 0.92 (0.80-0.97) and 0.65 (0.39-0.85) for PET, 0.96 (0.87-0.99) and 0.62 (0.43-0.78) for PET (SUV max >3.5), 0.98 (0.00-1.00) and 0.76 (0.02-1.00) for CT, and 0.80 (0.58-0.92) and 0.89 (0.57-0.98) for MRI.

3.1.2 Differentiating between precancerous or cancerous and benign lesions

Seven studies on the accuracy of imaging tests to differentiate between precancerous or cancerous versus benign lesions were found: EUS, EUS with FNA , EUS with FNA (CEA > 50 ng/ml), PET (standardized uptake values (SUV) max 2.4), CT and MRI. Only one study was found for each of these, except for EUS FNA, for which two were found. The median pre-test probability of a malignant lesion in these studies was 71% (range 52 to 75%). The estimates of sensitivity and specificity from these studies were as follows: 0.92 (0.74-0.98) and 0.60 (0.31-0.83) for EUS, 0.73 (0.01-1.00) and 0.94 (0.15-1.00) for EUS FNA (cytology), 0.29 (0.08-0.64) and 0.25 (0.05-0.70) for EUS FNA (CEA > 50 ng/ml), 0.94 (0.74-0.99) and 0.93 (0.69-0.99) for PET (SUV max 2.4), 0.62 (0.45-0.76) and 0.64 (0.39-0.84) for CT, and 0.93 (0.69-0.99) and 0.85 (0.58-0.96) for MRI.

It is difficult to make any conclusion on the basis of the results of the studies found in Best's SR because of the small number of available studies, and the small size of these studies, as well as due to serious methodological limitations of the studies related to patient selection, reference standard, and flow and timing. In particular, there is likely a problem with the selection of participants for such studies as all studies used surgical excision as the reference standard, suggesting that only patients with a high risk of malignancy were included.

3.2 Serum tumour markers in the diagnostic work-up of pancreatic lesions

3.2.1 Carbohydrate antigen 19-9 (CA 19-9)

One SR was found addressing the diagnostic accuracy of CA 19-9 for assessing malignancy in patients with a pancreatic lesion on imaging.[7] This review searched for studies published up to March 2016 and found 13 studies which contained a total of 1437 patients. Three of these studies were on any type of pancreatic cystic neoplasms (PCNs) and the rest were specifically on intraductal papillary mucinous neoplasms (IPMNs). The majority of studies in the review used a cut-off value of 37 u/ml for CA 19.9.

The estimated sensitivity and specificity were 0.47 (95% CI: 0.35-0.59) and 0.88 (95% CI: 0.86 - 0.91), respectively.

A search update revealed one additional study. This study by Gu et al. including 60 patients had estimates of sensitivity and specificity of 0.88 and 0.60, respectively at the cut-off of 37 u/ml.[8] A hypothesis as to why these findings are not be in-line with the Cao et al. review is that it was not possible to rule out that this study was not a case-control design. Because of concerns that Gu et al. might be a case-control study, we did not update the meta-analysis by Cao et al.

In the SR there was a high variability of estimates of sensitivity between the studies and the authors were not able to identify the cause of this heterogeneity. While the specificity of around 88% for CA 19-9 is satisfactory, the sensitivity of 47% is too poor for this marker to be used as sole test.

3.2.2 Carcino Embryonal Antigen (CEA)

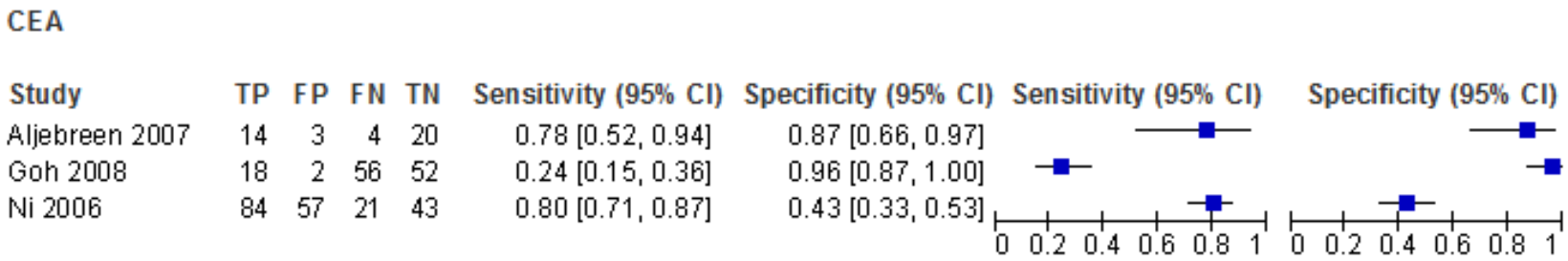
The search did not reveal any SRs on the accuracy of CEA for assessing malignancy in patients with focal pancreatic lesions. Therefore, a SR was performed (see appendix for details on search). In addition to the items specified in the RQ, an additional restriction regarding study design was that case-control studies were not accepted since these may not be applicable.

Three studies were identified: Aljebreen 2007[9], Goh 2008[11], and Ni 2005[10] The quality of these studies was assessed and a forest plot was constructed Figure 1. In total, these studies included 471 patients; 46, 220 and 205 respectively. These studies were conducted on patients with pancreatic lesions in hospitals in Canada, Singapore and China and included patients with a mean age of around 60 years.

Across the studies, 37% of the patients were diagnosed with malignant pancreatic cancer. CEA cut-offs were 3.1 nl/mL, 3.1 nl/mL and 5 nl/mL, respectively. All studies may have a higher risk patient population than in clinical practice because the authors selected either patients who had undergone operations[11] or biopsy with histologic examinations[9,10] for suspected pancreatic cancer.

Accuracy estimates varied widely across the studies. Because there were only three studies and a high heterogeneity, estimates were not summarized in a meta-analysis, but instead presented visually in a forest plot (Figure 1). Sensitivities ranged from 24% in the study by Goh et al. to 80% in the study by Ni et al. Specificities also showed heterogeneity, ranging from 43% in Ni et al. to 96% in Goh. The uncertainty around the accuracy of this test, including low estimates of sensitivity and specificity signal that this marker is not accurate enough to be used alone to diagnose malignancy in patients with focal pancreatic lesions.

Figure 1 – Forest plot for diagnostic test accuracy of serum CEA in diagnosing malignancy in patients with focal pancreatic lesions



TP: total positives, FP: false positives, FN: false negatives, TN: total negatives

Future research is needed to assess whether the combination of biomarkers leads to improved sensitivity while retaining acceptable specificity or if it may be useful in patients with lesions carrying a lower risk of malignancy, such as IPMNs. The fact that these tests are not sufficiently sensitive to guide clinical decisions, does not negate their potential value as prognostic tools.

3.3 Tests to assess curative resectability of pancreatic cancer

Two Cochrane SRs were found that addressed the diagnostic accuracy of tests for assessing curative resectability in patients with a pancreatic lesion on imaging: Allen et al and Tamburrino et al., both published in 2016.[2, 5] The review by Allen et al. focused on laparoscopy and found 16 studies. The review by Tamburrino *et al*. searched for accuracy studies on imaging tests (MRI, PET scan, and EUS performed as an add-on test or PET-CT as a replacement test to CT scanning), but unfortunately only found two small studies on EUS. No studies of on any other imaging modality were identified regarding the diagnostic accuracy for assessing resectabiltity.

3.3.1 Laparoscopy

The SR by Allen *et al*. assessed the role of laparoscopy after the diagnostic work-up of patients suspected of pancreatic cancer (and planned to receive curative resection) in predicting that disease was not resectable. The search was performed in May 2016 and found 16 primary studies which contained 1146 patients. Because the reference standard (histology) was also part of the index test (laparoscopy with histologic confirmation), false positives (FP) were not possible. Therefore, only sensitivity and post-test probability of unresectable disease were calculated. Pooled sensitivity was 0.64 (95% CI 0.50 to 0.77). At the median pre-test probability (prevalence) of unresectabilitiy of 0.41, the post-test probability of unresectability was 0.20 (95% CI 0.15 to 0.27), when laparoscopy indicates 'resectable disease'. This means that if a person is found to have disease on CT scan and laparoscopy indicates that the lesion is resectable, their probability of unresectable disease will be 20%. There was a very low consistency in the results and a high risk of bias across the studies. A limitation of these studies is that different definitions of unresectability were used, namely surgeon's judgment on unresectability was accepted when histopathological confirmation of liver or peritoneal involvement was not possible. Despite the poor methodological quality of the studies, the authors concluded that diagnostic laparoscopy appears to be beneficial in avoiding unnecessary laparotomies. On average, given a prevalence of unresectabiliy of 0.41, if laparoscopy is used in 100 patients where resection of cancer with curative intent is planned, it helps avoid unnecessary laparotomies in 21 patients.

3.3.2 EUS

The SR by Tamburrino et al. assessed the role of EUS in predicting unresectability of disease. The search date of the review was November 2015. The overall risk of bias of the review was judged to be low, although the source of funding or support was not reported for each of the included studies. The review included two studies with a total of 34 patients, both of which reported sufficient data to calculate sensitivity and specificity for unresectability. However, the planned analysis which considered a borderline category result of EUS was not possible as the review did not report this information. Both studies suffered from differential verification (different reference standards for different patients) and one of the studies had a high risk of bias due to only selecting patients with tumours of less than 3 cm in diameter. Because the results were similar between the studies, they were pooled. The pooled sensitivity for detecting non-resectable tumours was 0.87 (95% CI 0.54 to 0.97) and pooled specificity was 0.80 (95% CI 0.40 to 0.96). In a hypothetical study of 1000 patients and with a prevalence unresectability of 60.5% (average prevalence of two included studies) EUS prevents unnecessary surgery in 264 patients (95% CI 205 to 314). However, 146 patients (95% CI 96 to 205) will be incorrectly classified as being resectable (FN) and 79 patients (95% CI 16 to 237) will be incorrectly classified as unresectable (FP).

The authors concluded that there is significant uncertainty in the utility of EUS as a diagnostic tool for resectable pancreatic tumours detected on CT scan. They also state that there is "no evidence to suggest that it should be performed routinely in people with pancreatic cancer thought to have resectable disease on CT scan."

4 CONCLUSIONS,OTHER CONSIDERATIONS AND RECOMMENDATIONS

4.1 Conclusions

In patients suspected of pancreatic cancer,

- no firm conclusions can be drawn regarding the accuracy of imaging tests to diagnose malignancy of pancreatic cancer lesions.[6]
- serum biomarkers CA 19-9 and CEA lack sensitivity to be used as single test to diagnose malignancy of pancreatic cancer lesions (Cao 2016[7] for CA 19-9, and a three studies on CEA: Aljebreen 2007[9], Goh 2008[11], and Ni 2005[10])

In patients with potentially resectable pancreatic cancer lesions based on imaging tests (CT), no firm conclusions can be drawn regarding the accuracy of EUS for predicting curative resectability of pancreatic cancer lesions (Tamburrino 2016[5])

4.2 Other considerations

Factor	Comment
Balance between clinical benefits and harms	The Guideline Development Group (GDG) underlined that although the value of work-up to assess resectability was studied there was no formal research question on staging. Regarding laparoscopy the GDG noted that in some centres laparoscopic exploration and subsequent laparotomy or laparoscopic resection are systematically performed as one procedure. Due to differences in logistics and organisation this practise is not universal. The GDG pointed out that EUS is very operator dependent. The validators underlined the need to assess the tumour with EUS and FNA prior to intitiating chemotherapy.
Quality of evidence	Very low for recommendations 1,2,3,5,6 and very low to low for recommendation 4 The gap is striking between the available evidence based on number of subjects enrolled in clinical studies and the number of examinations performed in clinical practise.
Costs (resource allocation)	Cost was in general not considered in this guideline.
Patient preferences	Patient organisations were consulted in a Stakeholder meeting (see section 0.). They underlined the importance of open communication and information on benefits and harms in adapted language. Clinicians need to take patient preferences and their QoL into account when deciding on diagnostics.

4.3 Recommendations

Recommendation	Level of Evidence	Strength of recommendation
1. All patients suspected of pancreatic cancer should undergo diagnostic imaging with abdominal CT.	very low	strong
2. Diagnostic imaging with EUS, MRI, or PET scan should not routinely be used for differentiating benign from malignant lesions.	very low	weak
3. In cases in whom CT is inconclusive EUS (+/- FNA) or MRI should be used in an attempt to differentiate benign from malignant lesions.	very low	strong
4. Serum tumour markers CA 19-9 and CEA on their own are not indicated for the primary diagnosis of pancreatic cancer.	very low to low	strong
5. Laparoscopy should be considered in pancreatic cancer deemed resectable after high quality imaging, in order to avoid unnecessary laparotomies due to liver or peritoneal metastases.	very low	strong
6. EUS is not indicated for assessing resectability of pancreatic cancer.	very low	strong

5 APPENDIX

5.1 Search strategy

Update Cao 2016 and Systematic review on CEA

Search date: 5th December 2016

Appendix 1. Medline: 1181

#1 exp Pancreatic Neoplasms/ or ((pancrea* or exocrine) adj3 (fistula or lesion* or anastomosis or mass or neoplasm* or cancer* or carcinoma* or adenocarcinoma or cystadenocarcinoma or cyst* or tumour* or tumor* or malign*)).ti,ab,kf.

#2 exp CA-19-9 Antigen/ or exp Carcinoembryonic Antigen/ or (cd66e or CEA or "carcinoembryonic" or "carbohydrate antigen 19-9" or "carbohydrate antigen (CA) 19-9" or "CA 19-9" or "CA 19 9" or "CA 19.9" or "Carbohydrate antigen 19.9" or "CA19-9" or "CA19 9" or "CA19.9").ti,ab,kf.

#3 1 and 2

#4 exp "sensitivity and specificity"/ or exp "mass screening"/ or "reference values"/ or "false positive reactions"/ or "false negative reactions"/ or (specificit$ or screening or false positive$ or false negative$ or accuracy or predictive value$ or reference value$ or roc$ or likelihood ratio$).ti,ab,kf.

#5 3 and 4

#6 3 and 4

Appendix 2. EMBASE: 1190

#1 exp CA 19-9 antigen/ or carcinoembryonic antigen/ or (cd66e or CEA or "carcinoembryonic").ti,ab,kw,hw.

#2 exp pancreas tumor/ or ((pancrea* or exocrine) adj3 (fistula or lesion* or anastomosis or mass or neoplasm* or cancer* or carcinoma* or adenocarcinoma or cystadenocarcinoma or cyst* or tumour* or tumor* or malign*)).ti,ab,kw.

#3 exp "sensitivity and specificity"/

#4 exp screening/

#5 reference value/

#6 exp false positive result/

#7 exp false negative result/

#8 predictive value/

#9 exp diagnostic test accuracy study/

#10 (specificit$ or screening or false positive$ or false negative$ or accuracy or predictive value$ or reference value$ or roc$ or likelihood ratio$).ti,ab,kw.

#11 or/3-10

#12 1 and 2

#13 11 and 12

#14 (elsevier or canadian or embase).cr.

#15 13 and 14

#16 limit 15 to (conference abstract or conference paper or conference proceeding or "conference review")

#17 15 not 16

Update Allen 2016 (from May 2016)

Search date: 15th November 2016

Appendix 1. Cochrane Register of Diagnostic Test Accuracy Studies and CENTRAL search strategy: 191; Additional: 44

#1 ((ampulla near/2 vater*) or ampullovateric or (papilla near/2 vater*) or periampulla* OR peri-ampulla* OR choledoch* or alcholedoch* or bile duct* or biliary or cholangio* or gall duct or duoden* or small bowel or small intestin* or enter* or pancrea*)

#2 (carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malign*)

#3 (#1 AND #2)

#4 (pancreatect* OR pancreaticojejunost* OR pancreaticogastros* OR pancreaticoduodenect* OR duodenopancreatectom*)

#5 (#3 OR #4)

#6 (laparoscop* or peritoneoscop* or celioscop* or coelioscop*)

#7 (#5 AND #6)

Appendix 2. MEDLINE search strategy: 5228; Additional references: 237

(((((ampulla vateri[tiab] OR "Ampulla of Vater" [Mesh] OR ampullovateric[tiab] OR papilla vateri[tiab] OR vater papilla[tiab] OR vater ampulla[tiab] OR peri-ampull*[tiab] OR periampull*[tiab] OR choledoch*[tiab] OR alcholedoch*[tiab] OR bile duct*[tiab] OR biliary[tiab] OR cholangio*[tiab] OR gall duct[tiab] OR duodenum[tiab] OR duodenal[tiab] OR duoden*[tiab] OR small bowel[tiab] OR small instestin*[tiab] OR enteral[tiab] OR enteric[tiab] OR enter*[tiab] OR pancreatic[tiab] OR pancreato*[tiab] OR pancreas*[tiab]) AND (carcinoma[tiab] OR carcinomas[tiab] OR carcin*[tiab] OR cancer*[tiab] OR neoplas*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumorous[tiab] OR tumour*[tiab] OR tumor*[tiab] OR cyst[tiab] OR cysts[tiab] OR cystic[tiab] OR cyst*[tiab] OR growth*[tiab] OR adenocarcin*[tiab] OR malignant[tiab] OR malignancy[tiab])) OR "Duodenal Neoplasms"[Mesh] OR "Pancreatic Neoplasms"[Mesh] OR "Common Bile Duct Neoplasms"[Mesh]) AND (surger*[tiab] OR operat*[tiab] OR resection*[tiab] OR surgical*[tiab] OR Surgical Procedures, Operative[MeSH] OR General Surgery[MeSH])) OR (pancreatect*[tiab] OR pancreaticojejunost*[tiab] OR pancreaticogastros*[tiab] OR pancreaticoduodenect*[tiab] OR duodenopancreatectom*[tiab] OR Pancreatectomy[MeSH] OR Pancreaticojejunostomy[MeSH] OR Pancreaticoduodenectomy[MeSH])) AND (laparoscop*[tiab] OR peritoneoscop*[tiab] OR celioscop*[tiab] OR coelioscop*[tiab] OR "Laparoscopy"[Mesh])

Appendix 3. EMBASE search strategy: 4460: Additional references: 871

1 ((ampulla vateri or ampullovateric or papilla vateri or vater papilla or vater ampulla or periampull* or peri-ampull* or choledoch* or alcholedoch* or bile duct* or biliary or cholangio* or gall duct or duoden* or small bowel or small intestin* or enter* or pancrea*) and (carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malign*)).ti,ab.

2 exp duodenum cancer/ or Vater papilla tumor/ or exp pancreas cancer/ or exp bile duct tumor/

3 1 or 2

4 (surger* or surgical* or operat* or resection*). ti,ab.

5 exp Surgery/

6 4 or 5

7 3 and 6

8 (pancreatect* OR pancreaticojejunost* OR pancreaticogastros* OR pancreaticoduodenect* OR duodenopancreatectom*). ti,ab.

9 exp pancreas surgery/

10 7 or 8 or 9

11 (laparoscop* or peritoneoscop* or celioscop* or coelioscop*). ti,ab.

12 laparoscopy/ or laparoscopic surgery/

13 11 or 12

14 10 and 13

Appendix 4. Science Citation Index search strategy: 4375 (additional references: 292)

#1 TS=(((ampulla vateri or ampullovateric or papilla vateri or vater papilla or vater ampulla or periampull* or peri-ampull* or choledoch* or alcholedoch* or bile duct* or biliary or cholangio* or gall duct or duoden* or small bowel or small intestin* or enter* or pancrea*) and (carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malign*)))

#2 TS=(operat* OR surger* OR surgical* OR resection*)

#3 #1 AND #2

#4 TS=(pancreatect* OR pancreaticojejunost* OR pancreaticogastros* OR pancreaticoduodenect* OR duodenopancreatectom*)

#5 #3 OR #4

#6 TS=(laparoscop* or peritoneoscop* or celioscop* or coelioscop*)

#7 #5 AND #6

Update Tamburrino 2016 (from November 2015)

Search date: 15th November 2016

Appendix 1. MEDLINE (OvidSP) search strategy: 9763 – updated: 10080

1. (ampulla vateri or ampullovateric or papilla vateri or vater papilla or vater ampulla or periampull* or peri-ampull* or choledoch* or alcholedoch* or bile duct* or biliary or cholangio* or gall duct or duoden* or small bowel or small intestin* or enter* or pancrea*).ti,ab.

2. exp "Ampulla of Vater"/su [Surgery]

3. 1 or 2

4. (carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malign*).ti,ab.

5. 3 and 4

6. Duodenal Neoplasms/su [Surgery]

7. exp Pancreatic Neoplasms/su [Surgery]

8. Common Bile Duct Neoplasms/su [Surgery]

9. 5 or 6 or 7 or 8

10. (surger* or surgical* or operat* or resection* or preoperative).ti,ab.

11. exp Surgical Procedures, Operative/ or General Surgery/

12. 10 or 11

13. 9 and 12

14. (pancreatect* or pancreaticojejunost* or pancreaticogastros* or pancreaticoduodenect* or duodenopancreatectom* or pancreato-biliary).ti,ab.

15. pancreatectomy/ or pancreaticoduodenectomy/ or pancreaticojejuno stomy/

16. 13 or 14 or 15

17. (PET or MRI or NMRI or zeugmatogra* or ((emission or positron or magneti* or MR or NMR or proton or acoustic or ARFI) and (tomogra* or scan or scans or imaging))).ti,ab.

18. Positron-Emission Tomography/

19. exp Magnetic Resonance Imaging/

20. 17 or 18 or 19

21. Endosonography/

22. (endosonogra* or EUS).ti,ab.

23. (echogra* or ultrason* or ultrasound).ti,ab.

24. exp Ultrasonography/

25. 23 or 24

26. endoscop*.ti,ab.

27. exp Endoscopy/

28. 26 or 27

29. 25 and 28

30. 20 or 21 or 22 or 29

31. 16 and 30

32. sensitiv:.mp. OR diagnos:.mp. OR di.fs.

33. 31 and 32

Appendix 2. EMBASE (OvidSP) search strategy: 8097; updated: 8833

1. ((ampulla vateri or ampullovateric or papilla vateri or vater papilla or vater ampulla or periampull* or peri-ampull* or choledoch* or alcholedoch* or bile duct* or biliary or cholangio* or gall duct or duoden* or small bowel or small intestin* or pancrea*) and (carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malign*)).ti,ab.

2. exp duodenum cancer/su [Surgery]

3. Vater papilla tumor/su [Surgery]

4. exp pancreas cancer/su [Surgery]

5. exp bile duct tumor/su [Surgery]

6. 1 or 2 or 3 or 4 or 5

7. (surger* or surgical* or operat* or resection* or preoperative).ti,ab.

8. exp Surgery/

9. 7 or 8

10. 6 and 9

11. (pancreatect* or pancreaticojejunost* or pancreaticogastros* or pancreaticoduodenect* or duodenopancreatectom* or pancreato-biliary).ti,ab.

12. exp pancreas surgery/

13. 10 or 11 or 12

14. (PET or MRI or NMRI or zeugmatogra* or ((emission or positron or magneti* or MR or NMR or proton or acoustic or ARFI) and (tomogra* or scan or scans or imaging))).ti,ab.

15. positron emission tomography/di

16. exp nuclear magnetic resonance imaging/di

17. 14 or 15 or 16

18. endoscopic echography/

19. (endosonogra* or EUS).ti,ab.

20. (echogra* or ultrason* or ultrasound).ti,ab.

21. exp ultrasound/

22. 20 or 21

23. endoscop*.ti,ab.

24. exp gastrointestinal endoscopy/

25. 23 or 24

26. 22 and 25

27. 17 or 18 or 19 or 26

28. 13 and 27

29. di.fs. OR predict:.tw. OR specificity.tw.

30. 28 and 29

Appendix 3. Science Citation Index (Web of Knowledge) search strategy: 5412; updated: 5822

#1 TS=(((ampulla vateri or ampullovateric or papilla vateri or vater papilla or vater ampulla or periampull* or peri-ampull* or choledoch* or alcholedoch* or bile duct* or biliary or cholangio* or gall duct or duoden* or small bowel or small intestin* or pancrea*) and (carcin* or cancer* or neoplas* or tumour* or tumor* or cyst* or growth* or adenocarcin* or malign*)))

#2 TS=(operat* OR surger* OR surgical* OR resection* OR preoperative)

#3 #1 AND #2

#4 TS=(pancreatect* OR pancreaticojejunost* OR pancreaticogastros* OR pancreaticoduodenect* OR duodenopancreatectom* OR pancreato-biliary)

#5 #3 OR #4

#6 TS=(PET OR MRI OR NMRI OR zeugmatogra* OR ((emission OR positron OR magneti* OR MR OR NMR OR proton OR acoustic OR ARFI) AND (tomogra* OR scan OR scans OR imaging)) OR endosonogra* OR EUS OR ((echogra* OR ultrason* OR ultrasound) AND endoscop*))

#7 #5 AND #6

Appendix 4. National Institute for Health Research - Health Technology Assessment (Centre for Reviews and Dissemination): 70 (4 duplicates)

pancrea* AND accuracy: 70 updated: 70

periampullary AND accuracy: 4 updated: 4

5.2 Study selection

Figure 2 – Study flow of selection of primary diagnostic accuracy studies regarding laparoscopy (update Allen, 2016)

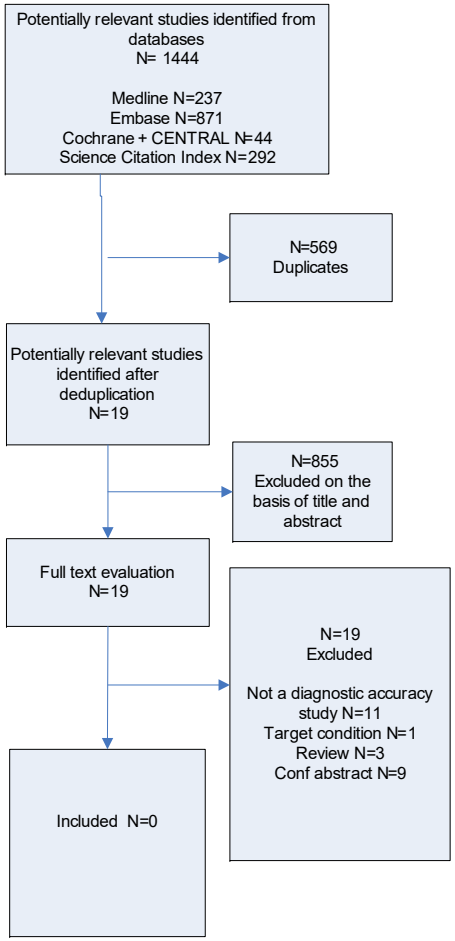


Figure 3 – Study flow of selection of primary diagnostic test accuracy studies regarding EUS (update Tamburrino)

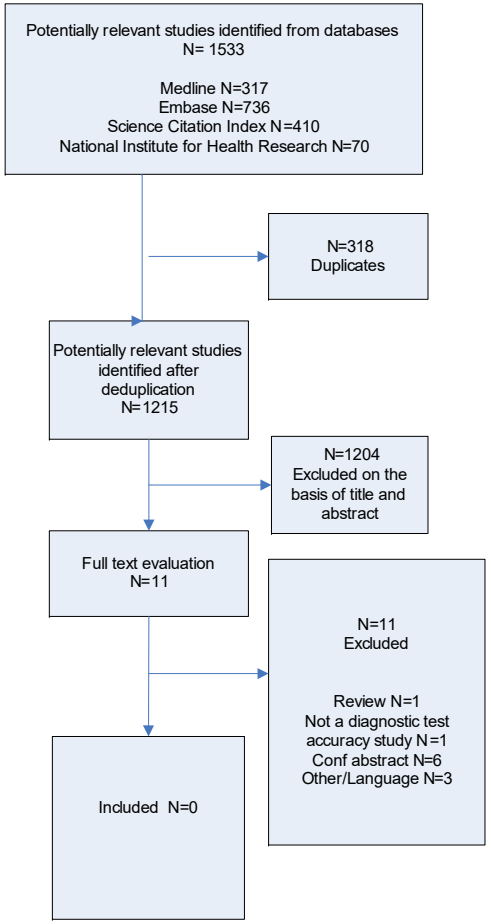


Figure 4 – Study flow selection of primary diagnostic test accuracy studies regarding CA 19-9 (update Cao)

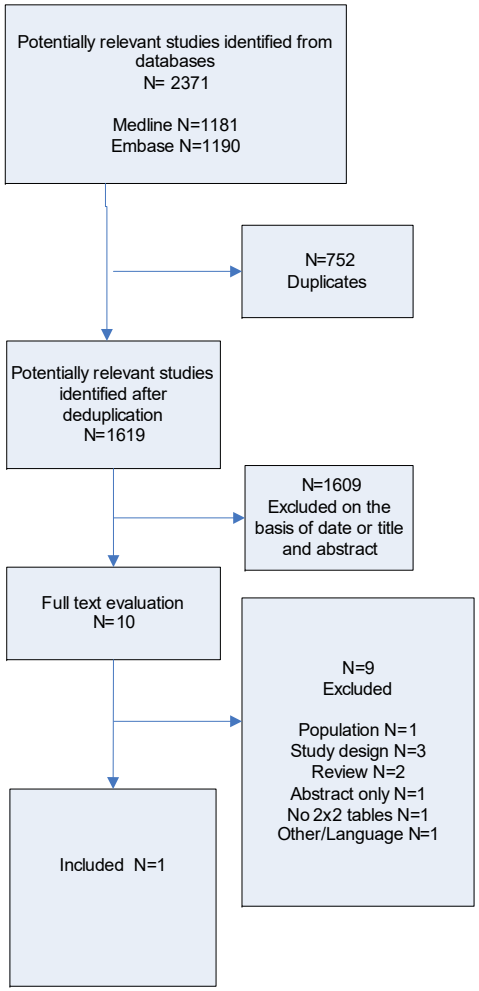


Figure 5 – Study flow of selection of primary diagnostic test accuracy studies regarding CEA

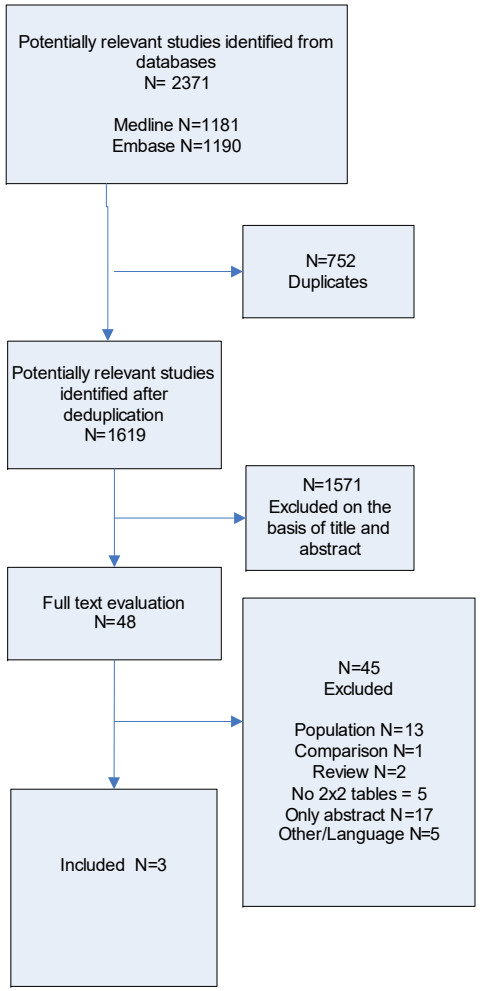


Table 4 – Excluded primary studies regarding laparoscopy (update Allen 2016; n= 20)

Reference	Reasons
Allen, 2016[2]	Systematic review (already included)
Arumugam, 2016[12]	Narrative review
Belgaumkar, 2016[13]	Not a diagnostic test accuracy study
Boogerd, 2016 [14]	Hepatic tumours / not addressing resectability
Butt, 2016 [15]	Not a diagnostic test accuracy study
Delitto, 2016[16]	Not a diagnostic test accuracy study
Dwyer, 2016[17]	Not a diagnostic test accuracy study
Fernandez-Cruz, 2016[18]	Not a diagnostic test accuracy study
Fong, 2016 [19]	Conference abstract / not a diagnostic test accuracy study
Goto, 2016[20]	Conference abstract / not a diagnostic test accuracy study
Horner, 2016[21]	Conference abstract
Kim, 2016[22]	Not a diagnostic test accuracy study
Kocaay, 2016[23]	Review / not a diagnostic test accuracy study
Looijen, 2016[24]	Conference abstract
Lustosa, 2016[25]	Conference abstract / systematic review
Maehara, 2016[26]	Conference abstract / not a diagnostic test accuracy study
Mataki, 2016[27]	Conference abstract / not a diagnostic test accuracy study
Morikawa, 2016[28]	Conference abstract
Satoi, 2016[29]	Not a diagnostic test accuracy study
Suker, 2016[30]	Conference abstract

Table 5 – Excluded primary studies regarding EUS (update Tamburrino 2016; n= 11)

Reference	Reasons
Bailon Cuadrado, 2016[31]	Conference abstract
Chen, 2016[32]	Not an add-on test to CT
Durmus, 2016[33]	Not possible to calculate sensitivity and specificity
Ge, 2016[34]	Not a diagnostic test accuracy study
Ghaneh, 2016[35]	Conference abstract
Jamaluddin, 2016[36]	Conference abstract
Mian, 2016[37]	Conference abstract
Tamburrino, 2016[5]	Systematic Review (already included)
Wang, 2015[38]	Chinese
Wijetunga, 2016[39]	Conference abstract
Yu, 2016[40]	Conference abstract

Table 6 – Excluded primary studies regarding CA19-9 (update Cao; n= 9)

Reference	Reasons
Bergquist,2016[41]	On the value of CA 19-9 as a predictor for clinical outcome, not for diagnosis
Cao, 2016a[42]	Case-control
Cao, 2016b [7]	This review
Coppin,2016[43]	Case-control
Hogendorf,2016[44]	Only included patients who had undergone surgery. This population is at higher risk.
Krishna,2016[45]	Only presented the diagnostic odds ratio. Not possible to extract the 2x2 table.
Pang,2016 [46]	Case-control
Yako, 2016[47]	Systematic review.
Zhang,2016[48]	No PDF

Table 7 – Excluded primary studies regarding SR on CEA (n= 45)

Reference	Reasons
Araki, 1976 [49]	No PDF
Ballehaninna, 2016 [50]	Review
Bassi, 2002 [51]	Differential diagnosis between serous and mucinous cystic tumors
Benini, 1988 [52]	Wrong patients, did not select patients with pancreatic lesions
Bottger, 1996 [53]	Language, German
Budzynska, 2013 [54]	Target disease was pancreatobiliary cancer and it was not possible to extract results for pancreatic cancer alone.
Buffet, 1996 [55]	No PDF
Cerwenka, 1997 [56]	No PDF
Civardi, 1986 [57]	No PDF
Clave, 1999 [58]	Language, Spanish
Correa-Gallego, 2009 [59]	Retrospective study that only included patients with resected intraductal papillary mucinous neoplasms (IPMNs) who also had CEA measurements.
Del Favero, 1986 [60]	Case-control
Fabris, 1985 [60]	No PDF
Fitzgerald, 1978 [61]	Study looked at several different cancers and did not report results separately for pancreatic cancer.
Frena, 2000 [62]	Language, Italian, No PDF
Frenette, 1994 [63]	No PDF
Fritz, 2011 [64]	Wrong patient selection. Only included patients who underwent surgical resection.
Futakawa, 2000 [65]	Did not present accuracy results or data to calculate the 2x2 table
Halm, 2000 [66]	No PDF
Hamori, 1997 [67]	No PDF
Heptner, 1988 [68]	Language, German
Hogendorf, 2016 [44]	Results for CEA not presented. Not possible to reconstruct 2x2 tables.
Hwang, 2011 [69]	Wrong patient selection. Retrospectively selected all patients with IPMN. Tested for association between CEA and malignancy, but not possible to reproduce 2x2.
Kokhanenko, 2001 [70]	Language, Russian

McLaughlin, 1999 [71]	Wrong patient selection. Retrospectively selected all patients who had a CA 19.9 serum test. No data provided on accuracy of CEA.
Nakamura, 1985 [72]	No PDF
Natsios, 2015 [73]	Wrong patient selection. Only included patients who had a stent placed for biliary obstruction
Nugent,1974 [74]	No PDF*
Ohshio, 1990 [75]	No PDF
Pasanen, 1992 [76]	No PDF
Pasanen, 1993 [77]	Wrong participants. Included patients with jaundice, cholestasis, acute pancreatitis, abdominal pain, or otherwise suspected of pancreatic cancer.
Piva, 2000 [78]	CEA *mRNA* as opposed to CEA
Podolsky, 1981 [79]	No PDF*
Podolsky, 1984 [80]	Review
Ritts, 1994 [81]	Looked at added value of CEA to CA 19-9. Not possible to reconstruct 2x2 tables for accuracy of CEA alone.
Sandblom, 2008 [82]	Not possible to reconstruct 2x2 tables
Staab 1987 [83]	No PDF
Trape, 2015 [84]	Wrong participants. Included several cancers and results for CEA were not presented separately for the 8 pancreatic cancer patients.
Walsh, 2002 [85]	Wrong patient group.
Wang, 1986 [86]	Wrong participants. Patients suspected of pancreatic cancer (not only those with focal lesions)
Wang, 1990 [86]	No PDF
Wang, 2013 [87]	No PDF
Wang, 2014 [88]	Case-control
Williams, 1977 [89]	No PDF
Yamaguchi, 2004 [90]	wrong population (half post-operative and not possible to filter these patients out in the 2x2 table)

5.3 Critical appraisal

Table 8 – Methodological quality of the included systematic reviews (AMSTAR)

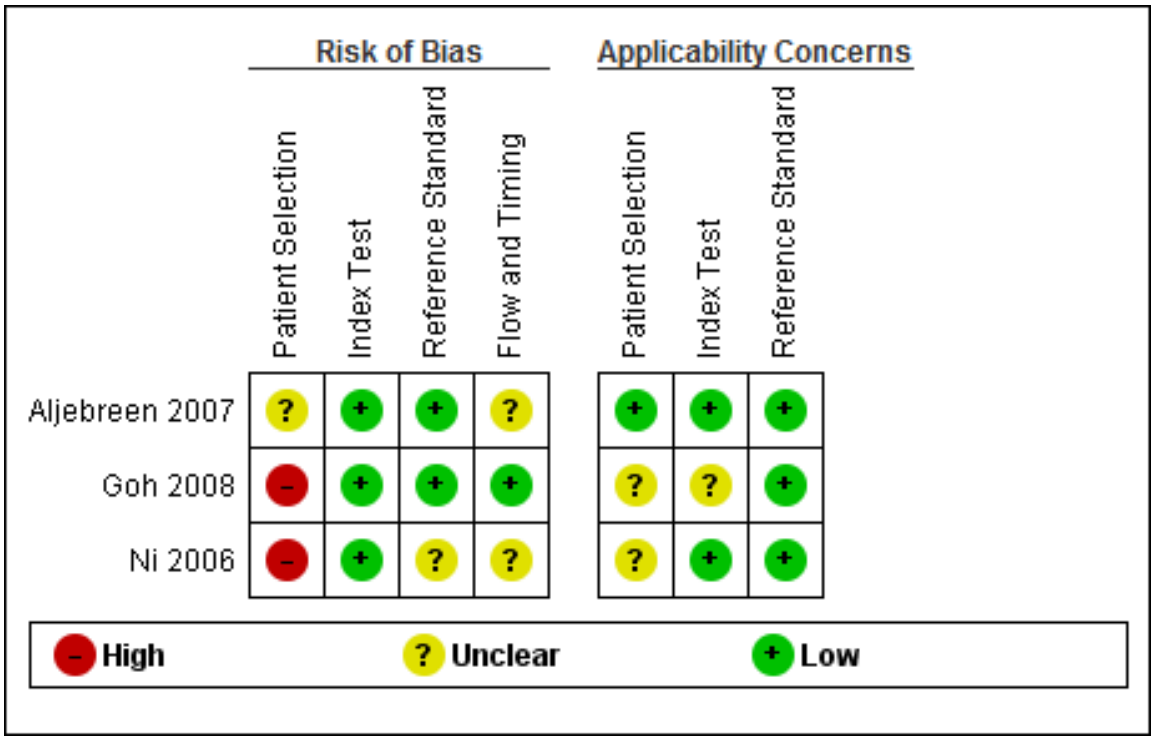
Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
Best 2016	yes	yes	yes	yes	yes	yes	yes	yes	yes	n/a*	no**
Allen 2016	yes	yes	yes	yes	yes	yes	yes	yes	yes	n/a*	no**
Tamburrino 2016	yes	yes	yes	yes	yes	yes	yes	yes	yes	n/a*	no**
Cao 2016	no	yes	no***	no	no	yes	yes	yes	yes	yes	no**

**Best planned to explore heterogeneity in results between publication vs. abstracts to explore the possibility of publication, but did not do so due to sparse data. Allen did not assess publication bias and argued that "Little is known about the mechanisms of publication bias for diagnostic accuracy studies and so it is not possible to estimate the impact of unpublished studies on our findings. Tamburrino did not assess publication bias as only 2 studies were included.*

***Sources of funding for review stated, but not for included studies*

**** Searched in two databases, but did not use a supplementary strategy*

Figure 6 – Quality assessment (QUADAS-2) for diagnostic test accuracy of serum CEA in diagnosing malignancy in patients with focal pancreatic lesions



5.4 Evidence tables

Table 9 – Evidence table of a SR regarding the diagnostic test accuracy of various imaging techniques to detect malignancy in patients with focal pancreatic lesions

Imaging modalities for characterising focal pancreatic lesions; Best 2016	
Methods	
• **Design**	*Cochrane systematic review*
• **Source of funding and competing interest**	*National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to the Upper Gastro-intestinal and Pancreatic Diseases Group and Cochrane-Hepato Biliary Group. No competing interests stated.*
• **Search date**	*19 July 2016*
• **Searched databases**	*Cochrane Register of Diagnostic Test Accuracy Studies. CENTRAL, MEDLINE, EMBASE and Science Citation*
• **Included study designs**	*Diagnostic test accuracy studies*
• **Number of included studies**	*53 studies (3118 patients), but not all studies were applicable to the research question*
• **Statistical analysis**	*Data from each study was summarised in two by two tables of TP, FP, TN, FN and used to calculate sensitivity and specificity. Univariate fixed or random models, where appropriate, were used for both sensitivity and specificity and no investigation of heterogeneity was performed. The HSROC model could not be fit.*
Patient characteristics	
• **Eligibility criteria**	*Adults with focal pancreatic lesions*
• **Exclusion criteria**	*none*
• **Patient & disease characteristics**	*No information provided*
Interventions	
• **Index test**	*CT scan, MRI scan, PET scan, EUS, EUS elastography, and EUS-guided biopsy either alone or in combination as replacement for major surgery for diagnostic purposes. They accepted the criteria stated by the authors to classify the lesion as benign, precancerous, and cancerous for different imaging modalities.*
• **Target condition**	*1. Benign versus precancerous and cancerous lesions (including the type of cancerous lesion).* *2. Benign and precancerous versus cancerous lesions.*

• **Reference standard**	*Histopathological examination of the entire lesion by surgical resection (gold standard). OR* *Histopathological examination (irrespective of how the tissues were obtained for histopathological examination) in patients with positive test (for cancerous or precancerous lesions) and clinical follow-up by a doctor (with or without sequential follow-up with imaging but using appropriate criteria such as metastases or confirmation of cancer by biopsy or death of patient due to cancer) of all patients with negative test for a period of at least six months and for a maximum period of 24 months.*
Results	
Diagnostic accuracy (sensitivity, specificity)	**Cancerous versus benign**
	EUS *0.95 (95% CI 0.84 to 0.99)* *0.53 (95% CI 0.31 to 0.74)*
	EUS FNA (cytology) *0.58 (95% CI 0.37 to 0.77)* *1.00 (95% CI 0.87 to 1.00)*
	PET (criteria unspecified) *0.92 (95% CI 0.80 to 0.97)* *0.65 (95% CI 0.39 to 0.85)*
	PET (SUV max > 3.5) *0.96 (95% CI 0.87 to 0.99)* *0.62 (95% CI 0.43 to 0.78)*
	CT *0.98 (95% CI 0.00 to 1.00)* *0.76(95% CI 0.02 to 1.00)*
	MRI *0.80 (95% CI 0.58 to 0.92)* *0.89 (95% CI 0.57 to 0.98)*
	Precancerous or cancerous versus benign
	EUS *0.92 (95% CI 0.74 to 0.98)* *0.60 (95% CI 0.31 to 0.83)*
	EUS FNA (cytology) *0.73 (95% CI 0.01 to 1.00)* *0.94 (95% CI 0.15 to 1.00)*
	EUS FNA (CEA > 50 ng/ml) *0.29 (95% C I0.08 to 0.64)* *0.25 (95% CI 0.05 to 0.70)*
	PET (SUV max 2.4) *0.94 (95% CI 0.74 to 0.99)* *0.93 (95% CI 0.69 to 0.99)*
	CT *0.62 (95% CI 0.45 to 0.76)* *0.64 (95% CI 0.39 to 0.84)*
	MRI *0.93 (95% CI 0.69 to 0.99)* *0.85 (95% CI 0.58 to 0.96)*
• **Limitations**	*The authors could not draw firm conclusions because of the difference in the way pancreatic lesions were defined into cancerous, precancerous, and benign. This resulted in many comparisons, which in turn mean that there were few studies per comparison, resulting in large confidence intervals. The overall methodological quality of the studies was poor, especially in terms of patient selection and flow and timing. All studies used surgical excision as the reference standard, suggesting that only patients with a high risk of malignancy were included.*

Table 10 – Evidence table of a SR regarding the diagnostic test accuracy of CA19-9 in diagnosing malignancy in patients with focal pancreatic lesions

Imaging modalities for characterising focal pancreatic lesions; Cao 2016	
Methods	
• **Design**	*Systematic review*
• **Source of funding and competing interest**	*The authors received no specific funding for this work*
• **Search date**	*1 March 2016*
• **Searched databases**	*Medline and Embase*
• **Included study designs**	*Cross-sectional diagnostic accuracy studies*
• **Number of included studies**	*N=13*
• **Statistical analysis**	*bivariate mixed-effects regression model, results presented in SROC*
Patient characteristics	
• **Eligibility criteria**	*(1) attempted to determine the benignity or malignancy of PCNs* *(2) sufficient information were provided to complete the 2×2 tables* *(3) histopathology results and/or clinical follow-up were used as the reference standard* *(4) they were published as full-text articles*
• **Exclusion criteria**	*(1) editorial, case reports, letter to editors, comment, brief communication or meeting abstract without publication of full article* *(2) <10 patients* *(3) overlapping data with other studies*
• **Patient & disease characteristics**	*Patients with focal lesions on imaging. Mean ages ranged between 54 and 66. 7 of the 13 studies were conducted in Asian patients.*
Interventions	
• **Index test**	*Serum Carbohydrate Antigen 19-9*
• **Target condition**	*Malignant pancreatic cystic neoplasms (including serous cystic adenomas (SCAs), cystic neuroendocrine tumors, mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs))*
• **Reference standard**	*histopathology results and/or clinical follow-up were used as the reference standard*

Results	
• **Diagnostic accuracy (sensitivity, specificity)**	*Sensitivity 0.47 (95% CI 0.35 to 0.59)* *Specificity 0.88 (95% CI 0.86 to 0.91)*
• **Limitations**	*High heterogeneity was found in our meta-analysis (particularly in sensitivity) and the meta-regression analyses failed to explore the main resources of heterogeneity among studies. A possible reason for the high heterogeneity between studies is that studies shared different cutoff values or definitions of malignant PCNs. The risks of bias in patient selection was high in 4/13 studies and unclear in 3/13 and it cannot be excluded that these studies were case-control studies.*

Table 11 – Evidence table of a primary study on the diagnostic test accuracy of CA19-9 in diagnosing malignancy in patients with focal pancreatic lesions

CA 19-9 for for characterising focal pancreatic lesions; Gu [8] **Application of 18F-FDG PET/CT combined with carbohydrate antigen 19-9 for differentiating pancreatic carcinoma from chronic mass-forming pancreatitis in Chinese elderly**	
• **Design**	*Retrospective cohort? Cross sectional ? Not reported*
• **Source of funding and competing interest**	*Not reported*
• **Setting**	*Presumably a hospital in China*
• **Sample size**	*60*
• **Time interval between tests**	*Not reported*
• **Statistical analysis**	*2x2 tables and Point estimates for sensitivity and specificity*
Patient characteristics	
• **Eligibility criteria**	*Patients with focal pancreatic lesions*
• **Exclusion criteria**	*Age under 65? It also seems like they only included patients with either pancreas cancer patients and chronic mass-forming pancreatitis*
• **Patient & disease characteristics**	*40 pancreas cancer patients* *20 chronic mass-forming pancreatitis* *Chinese Mean age approximately 90 years, 63% men, 15% diabetes, mean BMI 24*
Interventions	
• **Index test**	*>= 37 U/mL*
• **Reference standard**	*Diagnoses of all participants were confirmed by comprehensive methods including aspiration biopsy, surgical pathology, and clinical follow-up of 12 months.*

Results	
• **Diagnostic accuracy (sensitivity, specificity)**	*For Raised CA 19-9:* *Sens: 87.5%* *Spec: 60%* *Accuracy: 78%* *TP: 35, FP: 8, FN: 5, TN: 12*
Limitations and other comments	
• **Limitations**	*Although not stated, it is quite likely that this is a case-control design between pancreas cancer patients and chronic mass-forming pancreatitis.*

Table 12 – Evidence table of a primary study on the diagnostic test accuracy of CEA in diagnosing malignancy in patients with focal pancreatic lesions

CEA for characterising focal pancreatic lesions; Aljarbreen, 2007 [9] **Utility of endoscopic ultrasound, cytology and fluid carcinoembryonic antigen and CA 19-9 levels in pancreatic cystic lesions**	
• **Design**	*Cross sectional*
• **Source of funding and competing interest**	*Alberta Heritage Foundation of Medical Research*
• **Setting**	*Presumably patients in a hospital.*
• **Sample size**	*46*
• **Time interval between tests**	*Not specified*
• **Statistical analysis**	*Sens, spec, ppv and npv were analyzed.*
Patient characteristics	
• **Eligibility criteria**	*Pancreatic cystic lesion*
• **Exclusion criteria**	*Not specified*
• **Patient & disease characteristics**	*Final diagnosis: 41 (89%)* *23 (56%) surgical pathology* *23 (5%) benign lesion* *18 (44%) malignant/premalignant lesion*
Interventions	
• **Index test**	*Not pre-specified. The ideal cut-off values for the CEA and CA 19-9 were chosen by determining the cutoff closest to an ideal test (the upper left corner of the graph). Based on ROC curve: Cut-off value was 3.1 ng/mL.*

• **Reference standard**	*Based on surgical histopathology and/or imaging follow up of at least 12 mo, cysts were classified as benign versus malignant or pre-malignant. Only 41 (89%) of patients received a final diagnosis, so there may be some partial verification bias.*
Results	
• **Diagnostic accuracy (sensitivity, specificity)**	*CEA >3.1 nl/mL* *Sens: 70 (42-98)* *Spec: 85 (65-99)* *NPV: 79 (57-99)* *PPV: 78 (51-99)* *Accuracy: 78 (61-95)* *Area under the curve: 0.78 (0.54-0.93)*
Limitations and other comments	
• **Limitations**	*No predefined cut off point for CEA. 5/46 patients were not included in the analyses, presumably because they did not undergo histology. Was not possible to reconstruct the 2x2 table to get the exact accuracy reported.*

Table 12 continued:

CEA for characterising focal pancreatic lesions; Goh [11] **How Useful Are Clinical, Biochemical, and Cross-Sectional Imaging Features in Predicting Potentially Malignant or Malignant Cystic Lesions of the Pancreas? Results from a Single Institution Experience with 220 Surgically Treated Patients. Goh, 2008**	
• **Design**	*Retrospective cohort? Cross sectional ?*
• **Source of funding and competing interest**	*Not reported*
• **Setting**	*Department of Surgery, Singapore General Hospital*
• **Sample size**	*220*
• **Time interval between tests**	*Not reported*
• **Statistical analysis**	*Accuracy of each morphologic feature in diagnosing a potentially malignant, malignant, and benign cyst was also calculated using 2 by 2 contingency tables*
Patient characteristics	
• **Eligibility criteria**	*Patients who underwent operations for CLP or suspected CLP.* *CLP was considered to be symptomatic if it was identified on imaging performed for the evaluation of upper abdominal symptoms, such as upper abdominal pain or dyspepsia.*
• **Exclusion criteria**	*Not mentioned*

• **Patient & disease characteristics**	*Pseudocyst benign: 42* *Pseudocyst malignant: 2* *Operation for (suspected) cycstic neoplasm: 176* *Potentially malignant: 51* *Malignant: 55*
Interventions	
• **Index test**	*Cut off CEA not mentioned.*
• **Reference standard**	*Pathologically, the malignant potential of CLP was classified on the basis of the most aggressive histologic epithelial changes, according to the World Health Organization classification system. Tumors were considered malignant if carcinoma or carcinoma in situ was present.*
Results	
• **Diagnostic accuracy (sensitivity, specificity)**	*For Raised CEA:* *Sens: 18/74 (24%)* *Spec: 52/54 (96%)* *PPV: 18/20 (90%)* *NPV: 52/108 (48%)* *Accuracy: 70/128 (55%%)*
Limitations and other comments	
• **Limitations**	*Cut-of for 'raised CEA 'not mentioned. Patients selected in high risk population as they only included patients who underwent operations for suspicious pancreatic lesions.*

Table 12 continued:

CEA for for characterising focal pancreatic lesions; Ni 2005[10] The clinical value of serum CEA, CA19-9, and CA242 in the diagnosis and prognosis of pancreatic cancer	
Methods	
• **Design**	*Cross-sectional diagnostic accuracy study*
• **Source of funding and competing interest**	*National Natural Science Foundation of China*
• **Setting**	*Presumably patients at a hospital in Bejing with a suspicion of pancreatic cancer who also had histology performed*
• **Sample size**	*205, of which 105 had pancreatic cancer*
• **Time interval between tests**	*Not specified*
• **Statistical analysis**	*Sensitivity and specificity were calculated. The accuracy of combinations of serum markers was also investigated.*
Patient characteristics	
• **Eligibility criteria**	*Patients with a suspicion of pancreatic cancer (assume*
• **Exclusion criteria**	*No histopathology performed*
• **Patient & disease characteristics**	*Chinese, 36% female, 64% male, median age 61 (range: 20 to 82); of the patients with pancreatic cancer, there were 11 stage I, 69 stage II and 25 stage III patients, half had a tumour of >5cm*
Interventions	
• **Index test(s)**	*CEA using a cutoff of 5 ng/ml (also CA 19 and CA242)*
• **Reference standard**	*All diagnosis was confirmed by histological of post-operation or cytological of intraoperative biopsy examination*
Results	
• **Diagnostic accuracy (sensitivity, specificity)**	*Sensitivity 80 (95% CI 0.71-0.87)* *Specificity 43 (95% CI 0.33-0.53)* *84 TP, 57 FP, 21 FN, 43 TN*
Limitations and other comments	
• **Limitations**	*It is not clear whether this was a case-control study or a prospective cross-sectional study on patients with pancreatic lesions. In any case, there was a selection made based on patients who underwent histology, so the controls are not health patients or those with an entirely different disease. The diseases of the controls were islet cell carcinomas, ampulla of vater carcinomas, extrohepatic cholangiocarcinomas, and benign pancreatic diseases*

Table 13 – Evidence table of a SR regarding the diagnostic test accuracy of laparoscopy to predict curative tumour resection in patients with a focal pancreatic lesion on CT that is judged to be malignant (i.e. requires surgery)

Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer; Allen 2016	
Methods	
• **Design**	Cochrane systematic review
• **Source of funding and competing interest**	Funding from University College London, UK as this was part of a BSc project.
• **Search date**	15 May 2016
• **Searched databases**	(CENTRAL), MEDLINE via PubMed, EMBASE via OvidSP, Science Citation Index Expanded
• **Included study designs**	Diagnostic test accuracy studies
• **Number of included studies**	N=16
• **Statistical analysis**	Data from each study was summarised by TP and FN, which were used to calculate sensitivity. A meta-analysis of only sensitivities was performed by using a univariate random effects logistic regression model. The specificity of diagnostic laparoscopy in all studies was 1 because there were no false positives since laparoscopy and the reference standard are one and the same if histological examination after diagnostic laparoscopy is positive.
Patient characteristics	
• **Eligibility criteria**	People about to undergo curative resection for pancreatic and periampullary cancer with no contraindications (such as metastatic disease) for curative resection on CT scan, and who were anaesthetically fit to undergo major surgery.
• **Exclusion criteria**	None stated
• **Patient & disease characteristics**	Age ranged from 15-87 years, and there were approximately equal number of men and women. 7 studies only reported on patients with pancreatic cancer and 2 reported only on periampullary malignancies.
Interventions	
• **Index test**	Diagnostic laparoscopy with histologic confirmation
• **Target condition**	Unresectable pancreatic and periampullary cancers as defined by study authors (no existing consensus definition). In general, the cancer would not be resected if liver or peritoneal metastases were noted, or if the cancer had invaded important adjacent blood vessels that are beyond the criteria for borderline resectable cancers, for example greater than 180° involvement of the superior mesenteric artery.
• **Reference standard**	Histology (paraffin section confirming metastatic spread) from either laparoscopy or laparotomy or surgeon's judgment of unrepeatability on laparotomy. (Note: False positives were not possible because a positive index test, histologic confirmation during laparoscopy, is the same test as the reference standard, histology.)
Results	
• **Diagnostic accuracy (sensitivity, specificity, PPV, NPV, FNs, FPs)**	Sensitivity: 0.64 (95%CI 0.50 to 0.77)

Limitations	
• **Limitations**	All of the studies were of unclear or low methodological quality in one or more aspects, which may undermine the validity of the findings.

Table 14 – Evidence table of a SR regarding the diagnostic test accuracy of EUS to predict curative tumour resection in patients with a focal pancreatic lesion on CT (or on another imaging technique) that is judged to be malignant (i.e. requires surgery)

Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer; Tamburrino 2016	
Methods	
• **Design**	Cochrane systematic review
• **Source of funding and competing interest**	None known
• **Search date**	5 November 2015
• **Searched databases**	MEDLINE, EMBASE, Science Citation Index Expanded, and HTA (Health Technology Assessment)
• **Included study designs**	Diagnostic test accuracy studies
• **Number of included studies**	N=2
• **Statistical analysis**	Data from each study was summarised in two by two tables of TP, FP, TN, FN and used to calculate sensitivity and specificity. Univariate fixed effect models were used for both sensitivity and specificity and no investigation of heterogeneity was performed because there were only 2 studies.
Patient characteristics	
• **Eligibility criteria**	Adults considered for curative resection of pancreatic or periampullary cancer (on the basis of CT findings), who are fit to undergo major surgery.
• **Exclusion criteria**	None mentioned
• **Patient & disease characteristics**	A total of 34 patients were included over 2 studies. The mean ages were 61 and 64 years, the proportion of females was 24 and 65%, and the prevalence of unresectability was 0.53 and .78, respectively.
Interventions	
• **Index test**	MRI, PET scan, PET-CT scan, or EUS. However, only studies on EUS were found.
• **Target condition**	Unresectable pancreatic and periampullary cancers (any definition given unresectable was accepted)
• **Reference standard**	Histological confirmation of liver, peritoneal, or nodal metastatic involvement of suspicious (liver, peritoneal, or nodal metastatic) lesions obtained at diagnostic laparoscopy or laparotomy OR when biopsy is not possible, a surgeon's judgment of unresectability at laparotomy

Results	
• **Diagnostic accuracy (sensitivity, specificity, PPV, NPV, FNs, FPs)**	These estimates are given in terms of unresectability. Sensitivity: 0.87 (95% CI 0.54 to 0.97) Specificity: 0.80 (95% CI 0.40 to 0.96)
Limitations	
• **Limitations**	Only two small studies were found in this review and they were both on EUS. The methodological quality in one of the studies was as good as can be achieved ethically the methodological quality of the other study was largely unclear. Source of funding or support was not reported for each of the included studies. Applicability to our research question: both of the included studies are applicable to this research question.

5.5 GRADE tables

Table 15 – Summary of findings regarding the diagnostic accuracy of various imaging modalities for diagnosing cancerous pancreatic lesions (as opposed to benign lesions) in patients suspected of pancreatic cancer (median prevalence of cancerous lesions: 70%)

Test	No. of studies (No. of patients)	Sensitivity (95% CI)	Specificity (95% CI)	Predictive value of positive test (95% CI)	Predictive value of negative test (95% CI)	No. of False Positives* (95% CI)	No. of False Negatives* (95% CI)	GRADE LoE[a,b,c]
EUS	2 (133)	0.95 (0.84-0.99)	0.53 (0.31-0.74)	0.83 (0.74-0.90)	0.18 (0.03-0.55)	141 (78-207)	35 (7 to 112)	Very low
EUS FNA	2 (69)	0.58 (0.37-0.77)	1.00 (0.87-1.00)	1.00 (0.46-1.00)	0.49 (0.36-1.00)	0 (0 to 39)	294 (161 to 441)	Very low
PET	3 (99)	0.92 (0.80-0.97)	0.65 (0.39-0.85)	0.86 (0.75-0.94)	0.22 (0.08-0.54)	105 (45-183)	56 (21 to 140)	Very low
PET (SUV max >3.5)	1 (80)	0.96 (0.87-0.99)	0.62 (0.43-0.78)	0.85 (0.78-0.91)	0.13 (0.03-0.41)	114 (66-171)	28 (7 to 91)	Very low
CT	2 (123)	0.98 (0.00-1.00)	0.76 (0.02-1.00)	0.91 (0.00-1.00)	0.06 (0.00-1.00)	72 (0-294)	14 (1 to 700)	Very low
MRI	1 (29)	0.80 (0.58-0.92)	0.89 (0.57-0.98)	0.94 (0.76-0.99)	0.34 (0.16-0.63)	33 (6-129)	140 (56 to 294)	Very low

** Per 1000 patients tested*

a High risk of bias in most studies

b High concerns regarding applicability in most studies

c Imprecision due to low sample size(s) or vast heterogeneity (wide confidence intervals)

Table 16 – Summary of findings regarding the diagnostic accuracy of various imaging modalities for diagnosing precancerous or cancerous pancreatic lesions (as opposed to benign lesions) in patients suspected of pancreatic cancer (median prevalence of cancerous lesions:71%)

Test	No. of studies (No. of patients)	Sensitivity (95% CI)	Specificity (95% CI)	Predictive value of positive test (95% CI)	Predictive value of negative test (95% CI)	No. of False Positives* (95% CI)	No. of False Negatives* (95% CI)	GRADE LoE[a,b,c]
EUS	1 (34)	0.92 (0.74-0.98)	0.60 (0.31-0.83)	0.85 (0.72-0.93)	0.25 (0.05-0.67)	116 (49-200)	57 (14 to 185)	Very low
EUS FNA (cytology)	2 (52)	0.73 (0.01-1.00)	0.94 (0.15-1.00)	0.97 (0.03-1.00)	0.41 (0-0.94)	17 (0-246)	192 (0 to 703)	Very low
EUS FNA (CEA > 50 ng/ml)	1 (11)	0.29 (0.08-0.64)	0.25 (0.05-0.70)	0.49 (0.17-0.84)	0.87 (0.56-0.98)	217 (87-275)	504 (256 to 653)	Very low
PET (SUV max 2.4)	1 (32)	0.94 (0.74-0.99)	0.93 (0.69-0.99)	0.97 (0.85-1.00)	0.14 (0.02-0.48)	20 (3-90)	43 (7 to 185)	Very low
CT	1 (48)	0.62 (0.45-0.76)	0.64 (0.39-0.84)	0.81 (0.64-0.92)	0.59 (0.41-0.78)	104 (46-177)	270 (170 to 390)	Very low
MRI	1 (27)	0.93 (0.69-0.99)	0.85 (0.58-0.96)	0.94 (0.80-0.98)	0.17 (0.02-0.57)	43 (12-122)	50 (7 to 220)	Very low

** Per 1000 patients tested*

a High risk of bias in most studies

b High concerns regarding applicability in most studies

c Imprecision due to low sample size(s) or vast heterogeneity (wide confidence intervals)

Table 17 – Should CA 19-9 be used to diagnose malignant pancreatic tumours in patients with focal pancreatic lesions (Cao 2016)?

Sensitivity	0.47 (95% CI: 0.35 to 0.59)
Specificity	0.87 (95% CI: 0.84 to 0.90)

Prevalences	34%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 34%	
True positives (patients with malignant pancreatic tumours)	13 studies 489 patients	cohort & case-control type studies	serious [a]	serious [b]	very serious [c]	not serious	none	160 (119 to 201)	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having malignant pancreatic tumours)								180 (139 to 221)	
True negatives (patients without malignant pancreatic tumours)	13 studies 948 patients	cohort & case-control type studies	serious [a]	serious [b]	not serious	not serious	none	574 (554 to 594)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having malignant pancreatic tumours)								86 (66 to 106)	

a. The patient selection was not clear in several studies, indicating that about half of the studies may have had a case-control design
b. More than half the studies were in asian populations
c. High unexplained heterogeneity of results (I^2 – 81.87%)

Table 18 – Should laparoscopy be used to diagnose unresectability in pancreatic cancer (Allen 2016)?

Sensitivity	0.64 (95% CI: 0.50 to 0.77)
Specificity	1.00 (95% CI: 0.00 to 1.00)

Prevalences	41%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 41%	
True positives (patients with unresectability)	studies patients	cross-sectional (cohort type accuracy study)	very serious [1]	not serious	very serious [2]	very serious [3]	none	264 (205 to 314)	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having unresectability)								146 (96 to 205)	
True negatives (patients without unresectability)	studies patients	cross-sectional (cohort type accuracy study)	very serious [1]	not serious	very serious [4]	very serious [4]	none	590 (0 to 590)	⊕◯◯◯ VERY LOW
False positives (not possible) [4]								0 (0 to 590) [4]	

1. High risk of bias due to patient selection and flow and timing.
2. High heterogeneity between studies (estimates between 0.22-1)
3. Wide confidence intervals
4. Not possible to calculate specificity because false positives were not possible

Table 19 – Should EUS be used to diagnose unresectability in pancreatic cancer (Tamburrino 2016)?

Sensitivity	0.87 (95% CI: 0.54 to 0.97)
Specificity	0.80 (95% CI: 0.40 to 0.96)

Prevalences	60.5%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 60.5%	
True positives (patients with unresectability)	2 studies 23 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious	not serious	very serious [2]	none	526 (327 to 587)	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having unresectability)								79 (18 to 278)	
True negatives (patients without unresectability)	2 studies 11 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious	not serious	very serious [2]	none	316 (158 to 379)	⊕◯◯◯ VERY LOW
False positives (patients incorrectly classified as having unresectability)								79 (16 to 237)	

1. Both studies used surgeons' judgement on unresectability as the reference standard and so both the studies have unclear risk of bias in the 'reference standard' domain.
2. Only two very small studies

5.6 Stakeholder meeting

The Stakeholder meeting was held on February 20, 2017. Recommendations were scored (1-5) and discussed (Table 20). Patient organisations were consulted (Table 21).

Table 20 – Scoring of recommendations by Stakeholders

Diagnosis			Scores					Comments
Recommendations	Level of Evidence	Strength of recommendation	a	b	c	d	e	
1. All patients suspected of pancreatic cancer should undergo diagnostic imaging with abdominal CT.	very low	strong	5	5	5	5	5	why only abdomen? Thorax is needed as well
2. Diagnostic imaging with EUS, MRI, or PET scan should not routinely be used for differentiating benign from malign lesions.	very low	weak	5	5	4	5	4	only in selected cases
3. In cases in whom CT is inconclusive EUS (+/- FNA) or MRI should be used in an attempt to differentiate benign from malignant lesions.	very low	strong	5	5	4	5	5	
4. Serum tumour markers CA 19-9 and CEA are not indicated for the primary diagnosis of pancreatic cancer.	very low to low	strong	5	5		5	5	
5. Laparoscopy may be considered in pancreatic cancer deemed resectable after high quality imaging, in order to avoid unnecessary laparotomies due to liver or peritoneal metastases.	very low	weak	5	5	4	5	2	:"A tumour is resectable when the surgeon considers that it can be removed entirely"ASCO definition is "Primary surgical resection is recommended for all patients who have no metastases, appropriate performance and comorbidity profiles, and no radiographic interface between primary tumor and mesenteric vasculature " we can also say "resecability is discussed in multidisciplinary team", The additional value of diagnostic laparoscopy in PC is about 3-5%. In case resectable disease is found, laparoscopic resection of PC can de done in referral centres, with similar safety and efficacy as in open surgery
6. EUS is not indicated for assessing resectability of pancreatic cancer.	very low	strong	5	5	5	5	5	

Table 21 – Opinion of patient organisation

Voor Kom op tegen Kanker is het belangrijk dat de patiënt op elk ogenblik voldoende geïnformeerd wordt over zijn medische toestand, dit in een voor de patiënt begrijpelijke taal. Hierbij ook informatie over de behandelingsmogelijkheden met de voor- en nadelen. Ook dat de clinici rekening houden met de waarden en de voorkeuren van de patiënt. (p 21 van part 1, ook op p 30) Alsook dat hij of zij voldoende pychosociale ondersteuning krijgen alsook hun naasten. Er moet ook rekening gehouden worden met de kwaliteit van leven van de patiënt (komt niet terug in de uitgevoerde studies die geselecteerd werden, werd toen niet onderzocht)	Voor zeldzame tumoren zoals pancreaskanker er één is, is gebleken uit vroegere KCE studie dat de resultaten van de behandeling beter zijn in een ziekenhuis die meer dan 20 pancreasoperaties per jaar uitvoeren. Als Kom op tegen Kanker pleiten we voor expertise ziekenhuizen die preferentieel deze pathologie behandelen. (zie p 20 van part 1.) Dit was niet weerhouden vermits dit eerder een zaak is van de organisatie van zorg dan van good clinical practice guidelines.

REFERENCES

1. Peeters M, Vlayen J, Stordeur S, Mambourg F, Boterberg T, de Hemptinne B, et al. Scientific support of the College of Oncology: a national clinical practice guideline for pancreatic cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2009 16/02/2009. KCE Reports 105 Available from: https://kce.fgov.be/publication/report/scientific-support-of-the-college-of-oncology-a-national-clinical-practice-guidel
2. Allen VB, Gurusamy KS, Takwoingi Y, Kalia A, Davidson BR. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database Syst Rev. 2016;7:Cd009323.
3. Gurusamy KS, Davidson BR. Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database Syst Rev. 2015(2).
4. Gurusamy K, Davidson B. Imaging modalities for characterising focal pancreatic lesions. Cochrane Database of Systematic Reviews. 2012(11).
5. Tamburrino D, Riviere D, Yaghoobi M, Davidson BR, Gurusamy KS. Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database Syst Rev. 2016;9:Cd011515.
6. Best LR, V; Pereira, SP; Davidson, BR; Gurusamy, KS. Imaging modalities for characterising focal pancreatic lesions. Cochrane Database of Systematic Reviews. 2016.
7. Cao S, Hu Y, Gao X, Liao Q, Zhao Y. Serum Carbohydrate Antigen 19-9 in Differential Diagnosis of Benign and Malignant Pancreatic Cystic Neoplasms: A Meta-Analysis. PLoS ONE [Electronic Resource]. 2016;11(11):e0166406.

8. Gu X, Liu R. Application of 18F-FDG PET/CT combined with carbohydrate antigen 19-9 for differentiating pancreatic carcinoma from chronic mass-forming pancreatitis in Chinese elderly. Clinical Interventions In Aging. 2016;11:1365-70.

9. Aljebreen AM, Romagnuolo J, Perini R, Sutherland F. Utility of endoscopic ultrasound, cytology and fluid carcinoembryonic antigen and CA 19-9 levels in pancreatic cystic lesions. World Journal of Gastroenterology. 2007;13(29):3962-6.

10. Ni XG, Bai XF, Mao YL, Shao YF, Wu JX, Shan Y, et al. The clinical value of serum CEA, CA19-9, and CA242 in the diagnosis and prognosis of pancreatic cancer. European Journal of Surgical Oncology. 2005;31(2):164-9.

11. Goh BK, Tan YM, Thng CH, Cheow PC, Chung YF, Chow PK, et al. How useful are clinical, biochemical, and cross-sectional imaging features in predicting potentially malignant or malignant cystic lesions of the pancreas? Results from a single institution experience with 220 surgically treated patients. Journal of the American College of Surgeons. 2008;206(1):17-27.

12. Arumugam P, Balarajah V, Watt J, Abraham AT, Bhattacharya S, Kocher HM. Role of laparoscopy in hepatobiliary malignancies. Indian Journal of Medical Research. 2016;143(April):414-9.

13. Belgaumkar AP, Fuks D, Vimalraj V, Roy D, Gayet B. Laparoscopic pancreaticoduodenectomy with portal vein resection. Hpb. 2016;18:e800.

14. Boogerd LSF, Handgraaf HJM, Lam HD, Huurman VAL, Farina-Sarasqueta A, Frangioni JV, et al. Laparoscopic detection and resection of occult liver tumors of multiple cancer types using real-time near-infrared fluorescence guidance. Surgical Endoscopy and Other Interventional Techniques. 2016:1-10.

15. Butt MU, Osman H, Aderianwalla H, Hellums R, Furlough S, Jeyarajah D. Differences in pancreatic surgery management and techniques: A nationwide multi-institutional survey. Annals of Surgical Oncology. Conference: 69th Annual Cancer Symposium of the Society of Surgical Oncology Boston, MA United States. Conference Start: 20160302 Conference End: 20160305. Conference Publication: (var.pagings). 2016;23(1 suppl. 1):S174.

16. Delitto D, Luckhurst CM, Black BS, Beck JL, George TJ, Jr., Sarosi GA, et al. Oncologic and Perioperative Outcomes Following Selective Application of Laparoscopic Pancreaticoduodenectomy for Periampullary Malignancies. J Gastrointest Surg. 2016;20(7):1343-9.

17. Dwyer J, Pantanowitz L, Ohori NP, Pai RK, Vrbin C, Brand RE, et al. Endoscopic ultrasound-guided FNA and ProCore biopsy in sampling pancreatic and intra-abdominal masses. Cancer cytopathology. 2016;124(2):110-21.

18. Fernandez-Cruz L, Poves I, Pelegrina A, Burdio F, Sanchez-Cabus S, Grande L. Laparoscopic Distal Pancreatectomy for Pancreatic Tumors: Does Size Matter? Dig Surg. 2016;33(4):290-8.

19. Fong Z, Mehtsun W, Lillemoe K, Warshaw A, Fernandez-Del Castillo C, Chang DC, et al. The role of staging laparoscopy in patients with pancreatic adenocarcinoma: Withstanding the test of time? Annals of Surgical Oncology. 2016;1):S171-S2.

20. Goto T, Toyama H, Asari S, Terai S, Shirakawa S, Tanaka M, et al. Staging laparoscopy for pancreatic cancer. Journal of Gastroenterology and Hepatology (Australia). 2016;31:439-40.

21. Horner MP, Whalley A, Mowbray N, Brown TH, Al-Sarireh B. Staging laparoscopy for periampullary carcinoma at a tertiary pancreaticobiliary centre. Hpb. 2016;18:e777-e8.

22. Kim H, Song KB, Hwang DW, Lee JH, Shin SH, Jun ES, et al. A single-center experience with the laparoscopic Warshaw technique in 122 consecutive patients. Surgical Endoscopy and Other Interventional Techniques. 2016;30(9):4057-64.

23. Kocaay AF, Celik SU, Goktug UU, Cakmak A. A review on the role of laparoscopy in pancreatic cancer. Acta Gastro-Enterologica Belgica. 2016;79(2):233-8.

24. Looijen GA, Pranger BK, Derksen WMJ, De Jong KP, Pennings JP, Erdmann JI. The value of laparoscopic ultrasound during staging laparoscopy in patients with suspected pancreatic head cancer. Hpb. 2016;18:e390.

25. Lustosa S, Rezende A, Garani F, Farah J, Cavalcanti A, Goldenberg A, et al. Diagnostic test accuracy review of laparoscopy in pancreatic cancer. Hpb. 2016;18:e368.

26. Maehara J, Asai K, Watanabe M, Matsukiyo H, Saito T, Ishii T, et al. Short-term outcome of laparoscopic distal pancreatectomy. Surgical Endoscopy and Other Interventional Techniques. 2016;30:S429.

27. Mataki Y, Maemura K, Kurahara H, Kawasaki Y, Yonemori K, Sakoda M, et al. Examination of staging laparoscopy for advanced pancreatic cancer. Surgical Endoscopy and Other Interventional Techniques. 2016;30:S465.

28. Morikawa T, Ishida M, Ohtsuka H, Aoki T, Maeda S, Ariake K, et al. Evaluation of the safety and efficacy of staging laparoscopy for advanced pancreatic cancer. Surgical Endoscopy and Other Interventional Techniques. 2016;30:S430.

29. Satoi S, Yanagimoto H, Yamamoto T, Toyokawa H, Hirooka S, Yamaki S, et al. A clinical role of staging laparoscopy in patients with radiographically defined locally advanced pancreatic ductal adenocarcinoma. World Journal of Surgical Oncology. 2016;14 (1) (no pagination)(14).

30. Suker M, Groot Koerkamp B, Eskens FA, Nuyttens JJ, Van Eijck CHJ. High yield of occult metastases during staging laparoscopy for locally advanced pancreatic cancer. Hpb. 2016;18:e356-e7.

31. Bailon Cuadrado M, Rodriguez Lopez M, Perez Saborido B, Velasco Lopez R, Mambrilla Herrero S, Asensio Diaz E, et al. Accuracy for resectability and malignancy of FNA by use in pancreatic and periampullary lesions: Retrospective analysis in a Spanish HPB surgery unit. Hpb. 2016;18:e375.

32. Chen FM, Ni JM, Zhang ZY, Zhang L, Li B, Jiang CJ. Presurgical evaluation of pancreatic cancer: A comprehensive imaging comparison of CT versus MRI. American Journal of Roentgenology. 2016;206(3):526-35.

33. Durmus A, Yilmaz A, Malya F, Ozturk G, Bektasoglu H, Ertugrul G, et al. The Use of 18f-Fluorodeoxyglucose Positron Emission Tomography to Assess Clinical Outcomes of Patients with Borderline Resectable Pancreatic Cancer. Georgian Medical News. 2016(253):26-9.

34. Ge PS, Gaddam S, Keach JW, Mullady D, Fukami N, Edmundowicz SA, et al. Predictors for Surgical Referral in Patients With Pancreatic Cystic Lesions Undergoing Endoscopic Ultrasound: Results From a Large Multicenter Cohort Study. Pancreas. 2016;45(1):51-7.

35. Ghaneh P, Wong WL, Titman A, Plumpton C, Vinjamuri S, Johnson C, et al. PET-PANC: Multi-centre prospective diagnostic accuracy and clinical value trial of FDG PET/CT in the diagnosis and management of suspected pancreatic cancer. Journal of Clinical Oncology. Conference. 2016;34(no pagination).

36. Jamaluddin N, Kim S, Komanduri S, Reber HA, Hines OJ, Donahue TR, et al. Impact of EUS-FNA on the assessment of resectability following downstaging chemotherapy for locally advanced pancreatic cancer. Gastroenterology. 2016;1):S511.

37. Mian OY, Chen L, Narang A, Leal J, Rowe S, Rao AD, et al. Total lesion glycolysis as a predictor of pathologic outcomes locally advanced and borderline resectable patients undergoing surgery after preoperative stereotactic body radiation therapy. International Journal of Radiation Oncology Biology Physics. 2015;1):E184.

38. Wang L, Cheng X, Yu P, Du Y, Yang L, Chen L, et al. [Resectibility assessment of enhanced CT and contrast-enhanced endoscopic ultrasonography for the periampullary neoplasm]. Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal]. 2015;95(24):1921-4.

39. Wijetunga I, Chin SC, Young AL, Scarsbrook AF, Prasad KR. Pre-operative FDG PET-CT predicts outcome following curative-intent resection for peri-hilar cholangiocarcinoma; is routine FDG PET-CT indicated for all patients? Hpb. 2016;18:e679.

40. Yu P. Resectability assessment of enhanced CT and contrast-enhanced endoscopic ultrasonography for the periampullary neoplasm. Journal of Clinical Oncology. Conference. 2016;34(4 SUPPL. 1).

41. Bergquist JR, Puig CA, Shubert CR, Groeschl RT, Habermann EB, Kendrick ML, et al. Carbohydrate antigen 19-9 elevation in anatomically resectable, early stage pancreatic cancer is independently associated with decreased overall survival and an indication for neoadjuvant therapy: A national cancer database study. Journal of the American College of Surgeons. 2016;223(1):52-65.

42. Cao Z, Liu C, Xu J, You L, Wang C, Lou W, et al. Plasma microRNA panels to diagnose pancreatic cancer: Results from a multicenter study. Oncotarget. 2016;7(27):41575-83.

43. Coppin L, Benomar K, Corfiotti F, Cattan S, Renaud F, Lapere C, et al. CA-125, but not galectin-3, complements CA 19-9 for discriminating ductal adenocarcinoma versus non-malignant pancreatic diseases. Pancreatology. 2016;16(1):115-20.

44. Hogendorf P, Durczynski A, Skulimowski A, Kumor A, Poznanska G, Strzelczyk J. Neutrophil Gelatinase-Associated Lipocalin (NGAL) concentration in urine is superior to CA19-9 and Ca 125 in differentiation of pancreatic mass: Preliminary report. Cancer Biomarkers: Section A of Disease Markers. 2016;16(4):537-43.

45. Krishna SG, Bhattacharya A, Li F, Ross WA, Ladha H, Porter K, et al. Diagnostic Differentiation of Pancreatic Neuroendocrine Tumor From Other Neoplastic Solid Pancreatic Lesions During Endoscopic Ultrasound-Guided Fine-Needle Aspiration. Pancreas. 2016;45(3):394-400.

46. Pang L, Zhang N, Xia Y, Wang D, Wang G, Meng X. Serum APN/CD13 as a novel diagnostic and prognostic biomarker of pancreatic cancer. Oncotarget. 2016:24.

47. Yako YY, Kruger D, Smith M, Brand M. Cytokines as Biomarkers of Pancreatic Ductal Adenocarcinoma: A Systematic Review. PLoS ONE [Electronic Resource]. 2016;11(5):e0154016.

48. Zhang Y, Jiang L, Song L. Meta-analysis of diagnostic value of serum Carbohydrate antigen 199 in pancreatic cancer. Minerva Medica. 2016;107(1):62-9.

49. Araki A, Kawaharada M, Maeda S, Yachi A, Wada T. Clinical studies on carcinoembryonic antigen (CEA, gold) with reference to its diagnostic significance in cancer of digestive organs (Japanese). [Japanese]. Japanese Journal of Gastroenterology. 1976;73(4):384-94.

50. Ballehaninna UK, Chamberlain RS. Biomarkers for pancreatic cancer: promising new markers and options beyond CA 19-9. Tumour Biology. 2013;34(6):3279-92.

51. Bassi C, Salvia R, Gumbs AA, Butturini G, Falconi M, Pederzoli P. The value of standard serum tumor markers in differentiating mucinous from serous cystic tumors of the pancreas: CEA, Ca 19-9, Ca 125, Ca 15-3. Langenbecks Archives of Surgery. 2002;387(7-8):281-5.

52. Benini L, Cavallini G, Zordan D, Rizzotti P, Rigo L, Brocco G, et al. A clinical evaluation of monoclonal (CA19-9, CA50, CA12-5) and polyclonal (CEA, TPA) antibody-defined antigens for the diagnosis of pancreatic cancer. Pancreas. 1988;3(1):61-6.

53. Bottger T, Hassdenteufel A, Boddin J, Kuchle R, Junginger T, Prellwitz W. [Value of the CA 19-9 tumor marker in differential diagnosis of space-occupying lesions in the head of the pancreas]. Chirurg. 1996;67(10):1007-11.

54. Budzynska A, Nowakowska-Dulawa E, Marek T, Boldys H, Nowak A, Hartleb M. Differentiation of pancreatobiliary cancer from benign biliary strictures using neutrophil gelatinase-associated lipocalin. Journal of Physiology & Pharmacology. 2013;64(1):109-14.

55. Buffet C, Fourre C, Altman C, Prat F, Fritsch J, Choury A, et al. Bile levels of carcino-embryonic antigen in patients with hepatopancreatobiliary disease. European Journal of Gastroenterology & Hepatology. 1996;8(2):131-4.

56. Cerwenka H, Aigner R, Quehenberger F, Werkgartner G, Bacher H, Hauser H, et al. Preoperative differential diagnosis of benign and malignant pancreatic lesions - The value of pancreatic secretory trypsin inhibitor, Procarboxypeptidase B, CA19-9 and CEA. Hepato-Gastroenterology. 1997;44(16):1117-21.

57. Civardi G, Cerri L, Cavanna L. Diagnostic accuracy of a new tumor serologic marker, Ca 19-9: Comparison with CEA. Tumori. 1986;72(6):621-4.

58. Clave P, Boadas J, Gonzalez-Carro P, Mora J, Perez C, Martinez A, et al. [Accuracy of imaging techniques and tumor markers in the diagnosis of pancreatic cancer]. Gastroenterologia y Hepatologia. 1999;22(7):335-41.

59. Correa-Gallego C, Warshaw AL, Fernandez-del Castillo C. Fluid CEA in IPMNs: A useful test or the flip of a coin? American Journal of Gastroenterology. 2009;104(3):796-7.

60. Fabris C, Farini R, Piccoli A. CEA and ferritin in chronic pancreatic disease: A comparative evaluation. Hepato-Gastroenterology. 1985;32(3):146-8.

61. Fitzgerald PJ, Fortner JG, Watson RC, Schwartz MK, Sherlock P, Benua RS, et al. The value of diagnostic aids in detecting pancreas cancer. Cancer. 1978;41(3):868-79.

62. Frena A, Mazziotti A. Monoclonal antibody SPan-1 in detecting exocrine pancreatic carcinoma. [Italian]. Chirurgia. 2000;13(2):71-7.

63. Frenette PS, Thirlwell MP, Trudeau M, Thomson DM, Joseph L, Shuster JS. The diagnostic value of CA 27-29, CA 15-3, mucin-like carcinoma antigen, carcinoembryonic antigen and CA 19-9 in breast and gastrointestinal malignancies. Tumour Biology. 1994;15(5):247-54.

64. Fritz S, Hackert T, Hinz U, Hartwig W, Buchler MW, Werner J. Role of serum carbohydrate antigen 19-9 and carcinoembryonic antigen in distinguishing between benign and invasive intraductal papillary mucinous neoplasm of the pancreas. British Journal of Surgery. 2011;98(1):104-10.

65. Futakawa N, Kimura W, Yamagata S, Zhao B, Ilsoo H, Inoue T, et al. Significance of K-ras mutation and CEA level in pancreatic juice in the diagnosis of pancreatic cancer. Journal of Hepato-Biliary-Pancreatic Surgery. 2000;7(1):63-71.

66. Halm U, Rohde N, Klapdor R, Reith HB, Thiede A, Etzrodt G, et al. Improved sensitivity of fuzzy logic based tumor marker profiles for diagnosis of pancreatic carcinoma versus benign pancreatic disease. Anticancer Research. 2000;20(6D):4957-60.

67. Hamori J, Arkosy P, Lenkey A, Sapy P. The role of different tumor markers in the early diagnosis and prognosis of pancreatic carcinoma and chronic pancreatitis. Acta Chirurgica Hungarica. 1997;36(1-4):125-7.

68. Heptner G, Domschke S, Schneider MU, Domschke W. The new tumor-marker CA 72-4 in comparison with CA 19-9 and CEA in gastrointestinal disease. [German]. NUC Compact. 1988;19(4):132-4.

69. Hwang DW, Jang JY, Lim CS, Lee SE, Yoon YS, Ahn YJ, et al. Determination of malignant and invasive predictors in branch duct type intraductal papillary mucinous neoplasms of the pancreas: a suggested scoring formula. Journal of Korean Medical Science. 2011;26(6):740-6.

70. Kokhanenko N, Ignashov AM, Varga EV, Polkanova MS, Aleshina LA, Kimbarovskaia AA, et al. [Role of the tumor markers CA 19-9 and carcinoembryonic antigen (CEA) in diagnosis, treatment and prognosis of pancreatic cancer]. Voprosy Onkologii. 2001;47(3):294-7.

71. McLaughlin R, O'Hanlon D, Kerin M, Kenny P, Grimes H, Given HF. Are elevated levels of the tumour marker CA19-9 of any clinical significance?--an evaluation. Irish Journal of Medical Science. 1999;168(2):124-6.

72. Nakamura K, Kituta T, Takahashi T, Nakamura Y, Nakajima Y. A new cancer marker: a possible cancer screening method based on the

suppression of phosphofructokinase by sera from cancer patients. Cancer Detection & Prevention. 1985;8(1-2):207-18.

73. Natsios A, Vezakis A, Kaparos G, Fragulidis G, Karakostas N, Kouskouni E, et al. Significance of serum and bile tumor markers in the diagnostic approach of patients with malignant pancreatobiliary disease. Journal of B.U.On. 2015;20(4):1030-6.

74. Nugent FW, Hansen ER. Radioimmunoassay of carcinoembryonic antigen. A diagnostic test for carcinoma of the colon and pancreas. Archives of Internal Medicine. 1974;134(1):59-61.

75. Ohshio G, Manabe T, Watanabe Y, Endo K, Kudo H, Suzuki T, et al. Comparative studies of DU-PAN-2, carcinoembryonic antigen, and CA19-9 in the serum and bile of patients with pancreatic and biliary tract diseases: evaluation of the influence of obstructive jaundice. American Journal of Gastroenterology. 1990;85(10):1370-6.

76. Pasanen PA, Eskelinen M, Partanen K, Pikkarainen P, Penttila I, Alhava E. A prospective study of the value of imaging, serum markers and their combination in the diagnosis of pancreatic carcinoma in symptomatic patients. Anticancer Research. 1992;12(6B):2309-14.

77. Pasanen PA, Eskelinen M, Partanen K, Pikkarainen P, Penttila I, Alhava E. Receiver operating characteristic (ROC) curve analysis of the tumour markers CEA, CA 50 and CA 242 in pancreatic cancer; results from a prospective study. British Journal of Cancer. 1993;67(4):852-5.

78. Piva MG, Navaglia F, Basso D, Fogar P, Roveroni G, Gallo N, et al. CEA mRNA identification in peripheral blood is feasible for colorectal, but not for gastric or pancreatic cancer staging. Oncology. 2000;59(4):323-8.

79. Podolsky DK, McPhee MS, Alpert E, Warshaw AL, Isselbacher KJ. Galactosyltransferase isoenzyme II in the detection of pancreatic cancer: comparison with radiologic, endoscopic, and serologic tests. New England Journal of Medicine. 1981;304(22):1313-8.

80. Podolsky DK. Serologic markers in the diagnosis and management of pancreatic carcinoma. World Journal of Surgery. 1984;8(6):822-30.

81. Ritts Jr RE, Nagorney DM, Jacobsen DJ, Talbot RW, Zurawski Jr VR. Comparison of preoperative serum CA19-9 levels with results of diagnostic imaging modalities in patients undergoing laparotomy for suspected pancreatic or gallbladder disease. Pancreas. 1994;9(6):707-16.

82. Sandblom G, Granroth S, Rasmussen IC. TPS, CA 19-9, VEGF-A, and CEA as diagnostic and prognostic factors in patients with mass lesions in the pancreatic head. Upsala Journal of Medical Sciences. 2008;113(1):57-64.

83. Staab HJ. The combined use of CA 19-9 and carcino-embryonic antigen (CEA) in malignancies of the gastrointestinal tract. Acta Gastroenterologica Belgica. 1987;50(1):29-35.

84. Trape J, Sala M, Franquesa F, Ordeig JM, Soler-Bel JM, Bustamante E, et al. Clinical utility of determining tumor markers in patients with signs and symptoms of cancer. Clinical Chemistry and Laboratory Medicine. 2015;53(3):485-91.

85. Walsh RM, Henderson JM, Vogt DP, Baker ME, O'Malley C M, Jr., Herts B, et al. Prospective preoperative determination of mucinous pancreatic cystic neoplasms. Surgery. 2002;132(4):628-33; discussion 33-4.

86. Wang JY, Chen FZ, Yang YZ. Evaluation of non-invasive diagnostic tests in detecting cancer of the pancreas. Chinese Medical Journal. 1990;103(10):817-20.

87. Wang YZ, Zhou YW, Xie XY, Li GN, Wang XH, Li FY, et al. The levels of carbohydrate antigen 19-9 are associated with gender and age in Chinese population. Clinical Laboratory. 2013;59(7-8):813-7.

88. Wang X, Li Y, Tian H, Qi J, Li M, Fu C, et al. Macrophage inhibitory cytokine 1 (MIC-1/GDF15) as a novel diagnostic serum biomarker in pancreatic ductal adenocarcinoma. BMC Cancer. 2014;14:578.

89. Williams RR, McIntire KR, Waldmann TA, Feinleib M, Go VL, Kannel WB, et al. Tumor-associated antigen levels (carcinoembryonic antigen, human chorionic gonadotropin, and alpha-fetoprotein) antedating the diagnosis of cancer in the Framingham study. Journal of the National Cancer Institute. 1977;58(6):1547-51.

90. Yamaguchi K, Nagano M, Torada N, Hamasaki N, Kawakita M, Tanaka M. [Urine diacetylspermine as a novel tumor marker for pancreatobiliary carcinomas]. Rinsho Byori - Japanese Journal of Clinical Pathology. 2004;52(4):336-9.