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Number 141

Imaging Tests for the Diagnosis and Staging of Pancreatic Adenocarcinoma



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Imaging Tests for the Diagnosis and Staging of Pancreatic Adenocarcinoma

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Imaging Tests for the Diagnosis and Staging of Pancreatic Adenocarcinoma

Structured Abstract

Objectives. Our objectives were to synthesize the available information on the diagnostic accuracy and clinical utility of commonly used imaging tests for the diagnosis and staging of pancreatic adenocarcinoma, as well as screening for pancreatic adenocarcinoma in high risk individuals.

Data sources. We searched Embase, MEDLINE, PubMed, and The Cochrane Library from 1980 through November 1, 2013, for English-language, full-length articles on the role of multidetector computed tomography (MDCT), endoscopic ultrasound with fine-needle aspiration (EUS-FNA), magnetic resonance imaging (MRI), and positron emission tomography–computed tomography (PET/CT) in screening, diagnosis, and staging pancreatic adenocarcinoma. The searches identified 9,776 citations; after screening against the inclusion criteria, we included 15 systematic reviews and 108 primary studies.

Methods. We extracted data from the included studies and constructed evidence tables. Comparative outcomes of interest included diagnostic accuracy (sensitivity and specificity), staging accuracy, screening accuracy, clinical management, quality of life, survival, and harms of imaging tests. For studies of a single imaging test, the key outcomes were accuracy and procedural harms. Where possible, we pooled the data using bivariate binomial regression models for comparative accuracy. For each pair of tests and each assessed aspect (e.g., determination of metastases), we determined whether the evidence was sufficient to permit a conclusion of a difference, a conclusion of similar accuracy, or neither (i.e., insufficient). We rated the risk of bias of individual studies using an internal validity instrument and graded the overall strength of evidence of conclusions using Evidence-based Practice Center methods. For data on single-test accuracy, procedural harms, patient tolerance, and screening accuracy, we tabulated the important information and summarized the evidence qualitatively.

Results. We included 15 systematic reviews and 108 primary studies. Regarding comparative accuracy, the evidence was sufficient to conclude that MDCT and EUS-FNA have similar accuracy in assessing resectability in patients whose disease is unstaged, and that EUS-FNA has a slight advantage over MDCT with respect to T (tumor) staging (specifically, a lower chance of undersizing the tumor). Further, we concluded that MDCT and MRI are similarly accurate with respect to both diagnosing and assessing vessel involvement. For PET/CT, evidence was generally inconclusive, but we found low-strength evidence to conclude that PET/CT is more accurate than MDCT in assessing distant metastases (slight advantages in both sensitivity and specificity). None of the included studies reported comparative data on clinical management, survival, quality, or the impact on comparative accuracy of patient characteristics, tumor characteristics, or operator experience. Many studies have reported procedural harms, but harms are generally rare and are different for different imaging modalities. In the screening of people at high risk of developing pancreatic adenocarcinoma, available studies do not correlate the results of a given imaging test to subsequent diagnoses.

Conclusions. Current evidence permits some tentative conclusions about the comparative assessment of imaging tests for diagnosing and staging pancreatic adenocarcinoma, but many gaps remain. The conclusions we did draw are as follows: MDCT and EUS-FNA have similar accuracy in assessing resectability in patients whose disease is unstaged; EUS-FNA has a slight advantage over MDCT with respect to T (tumor) staging (specifically, a lower chance of undersizing the tumor); MDCT and MRI are similarly accurate with respect to both diagnosing and assessing vessel involvement; and PET/CT is more accurate than MDCT in assessing distant metastases (slight advantages in both sensitivity and specificity). The prominent gaps include minimal information on MDCT angiography, imprecise data on other imaging techniques, a lack of comparative data on patient-oriented outcomes and factors that could influence comparative accuracy, and test-specific data on screening accuracy.

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Abbreviations used above:

ES	– Executive Summary
EUS-FNA	– Endoscopic ultrasound with fine needle aspiration
MDCT	– Multidetector computed tomography
MRI	– Magnetic resonance imaging
PET-CT	– Positron emission tomography combined with computed xiiomography
PICO	– Patients, interventions, comparators, outcomes
ROC	– Receiver Operating Characteristics curve

Executive Summary

Background

Pancreatic Adenocarcinoma

Pancreatic cancer is the fourth most common cause of cancer death among men and women in the United States.^{1,2} In 2013 in the United States, about 46,000 people received a diagnosis of pancreatic cancer and 40,000 died of the disease.³ Risk factors for pancreatic cancer include tobacco use; personal history of chronic pancreatitis, diabetes, or obesity; and a family history of pancreatic cancer.¹ About 10 percent of patients with pancreatic cancer have a positive family history of the disease.⁴ Pancreatic cancer incidence rates were reportedly highest among African American men (21.3 per 100,000) and women (17.6 per 100,000) during 2004 and 2008.¹ The second highest rates were reported for Caucasian men (16.8 per 100,000) and women (12.8 per 100,000).¹ The differences between these populations and burden of disease may be related to higher rates of cigarette smoking and diabetes mellitus among African American men than for Caucasian men and higher body mass indexes among African American women than for Caucasian women.¹

Diagnosis and Staging

Patients with early pancreatic cancer are often asymptomatic or have only nonspecific symptoms such as malaise, fatigue, and appetite loss. As a result, patients often present with advanced stage disease when weight loss, jaundice, and severe abdominal pain often appear. Due to this delayed diagnosis, approximately 80 percent to 85 percent of cases are too advanced to permit surgical resection,⁵ and the median survival patients with unresectable tumors is only 6–10 months.⁶

Given the poor prognosis of this disease, it is important for patients to understand differences in the ability of imaging modalities to diagnose pancreatic adenocarcinoma. Also, elucidating patients' experience and tolerance of various imaging modalities may help future patients weigh the benefits and harms of these tests and allow patients and their providers to incorporate individual values and priorities into the choice of imaging evaluation. Many patients are willing to experience some discomfort during an imaging test to ensure that their disease is appropriately diagnosed and staged. However, if two tests are equally accurate, test tolerance may be an important outcome.

Once pancreatic adenocarcinoma is diagnosed, staging the disease is critical and is the key determinant of clinical management, as well as a key predictor of survival. As noted, most cases are diagnosed at an advanced stage, precluding surgical resection.¹ When pancreatic adenocarcinoma is diagnosed at an advanced stage, the 5-year survival is approximately 2 percent. However, when pancreatic cancer is diagnosed at a localized stage, the 5-year survival is approximately 22 percent.¹

Currently, there are no widely accepted clinical practice guidelines with strong recommendations on which imaging modalities to use in the diagnosis and staging of pancreatic cancer.

Resectability

Surgical resection offers the only hope of cure and is typically determined via multidisciplinary consultation (e.g., surgeon, gastroenterologist, radiologist, medical oncologist, radiation oncologist) considering a variety of factors. The two key factors in assessing resectability are distant metastasis (which excludes resectability) and blood vessel involvement (which sometimes excludes unresectability, depending on the degree of involvement). The major blood vessels of focus are the celiac artery, common hepatic artery, superior mesenteric artery, superior mesenteric vein, and portal vein. The resectability criteria continue to evolve as surgical techniques advance and more tumors are resectable via reconstruction of blood vessels.⁷

Multidetector computed tomography (MDCT) scan is often the first imaging test in a patient whose symptoms suggest pancreatic adenocarcinoma. This widely available test provides three-dimensional (3D) multiplanar reconstruction images within a single breath-hold, enabling determination of tumor size, extent, and spread, with a standardized pancreas protocol.^{8,9} However, MDCT does not always differentiate malignant from benign pancreatic lesions, and its ability to detect small tumors or small hepatic/peritoneal metastases is limited. Another concern about MDCT, particularly when used for screening, is that the procedure exposes the patient to potential harm through ionizing radiation.

MDCT can be performed using standard technique, whereby a single scan is obtained during delayed (i.e., venous) phase of enhancement. MDCT can also be performed using angiographic technique whereby images are obtained using at least two scans during arterial and venous phases of enhancement to permit more confident identification of arteries for surgical mapping.

Other commonly used imaging technologies for diagnosing and staging pancreatic adenocarcinoma include endoscopic ultrasound with fine-needle aspiration (EUS-FNA), magnetic resonance imaging (MRI), and positron emission tomography–computed tomography (PET/CT). EUS-FNA provides image-guided tissue sampling by placement of an endoscope into the upper gastrointestinal tract. MRI is noninvasive and provides detailed information about soft tissues, including the pancreas, in multiple planes. PET/CT provides information about tissue function through radiotracers that can be anatomically localized through CT. However, PET/CT exposes patients to radiation, mainly through the administration of the radiotracer.

Screening

Screening for pancreatic adenocarcinoma is not recommended for the general population (e.g., the U.S. Preventive Services Task Force gives a D recommendation).¹⁰ However, some recommend screening people at high risk of developing pancreatic cancer, such as those having two or more first-degree relatives with pancreatic cancer or those carrying specific genetic risk factors, such as Peutz-Jeghers syndrome or carriers of *BRCA2*, *PALB2*, *p16* gene mutations.¹¹ The most suitable imaging technology for screening high-risk populations is unclear.

Objectives of This Review

Our objectives were to synthesize the available information on the diagnostic accuracy and clinical utility of various imaging tests for the diagnosis and staging of pancreatic adenocarcinoma, as well as screening for pancreatic adenocarcinoma. The availability of this information will assist clinicians in selecting imaging tests, may reduce variability across treatment centers in staging protocols, and may improve patient outcomes. A secondary objective is to identify gaps in the evidence base to inform future research needs.

Scope and Key Questions

The Key Questions (KQ) are listed below:

1. What is the comparative effectiveness of imaging techniques (e.g., MDCT, MDCT angiography, EUS-FNA, PET/CT, MRI) for *diagnosis* of pancreatic adenocarcinoma in adults with suspicious symptoms?
 - a. What is the accuracy of each imaging technique for diagnosis and assessment of resectability?
 - b. What is the comparative accuracy of the different imaging techniques for diagnosis and assessment of resectability?
 - c. What is the comparative diagnostic accuracy of using a single imaging technique versus using multiple imaging techniques?
 - d. How is test experience (e.g., operative experience, assessor experience, center's annual case volume) related to comparative diagnostic accuracy of the different imaging strategies?
 - e. How are patient factors and tumor characteristics related to the comparative diagnostic accuracy of the different imaging strategies?
 - f. What is the comparative clinical management after the different imaging strategies when used for diagnosis?
 - g. What is the comparative impact of the different imaging strategies on long-term survival and quality of life when used for diagnosis?
2. What is the comparative effectiveness of imaging techniques (e.g., MDCT, MDCT angiography, EUS-FNA, PET/CT, MRI) for *staging* of pancreatic adenocarcinoma among adults with a diagnosis of pancreatic adenocarcinoma?
 - a. What is the staging accuracy of each imaging technique (for tumor size, lymph node status, vessel involvement, metastases, stage I–IV, and resectability)?
 - b. What is the comparative staging accuracy among the different imaging techniques?
 - c. What is the comparative staging accuracy of using a single imaging technique versus using multiple imaging techniques?
 - d. How is test experience (e.g., operative experience, assessor experience, center's annual case volume) related to comparative staging accuracy of the different imaging strategies?
 - e. How are patient factors and tumor characteristics related to the comparative staging accuracy of the different imaging strategies?
 - f. What is the comparative clinical management of the different imaging strategies when used for staging?
 - g. What is the comparative impact of the different imaging strategies on long-term survival and quality of life when used for staging?
3. What are the rates of harms of imaging techniques (e.g., MDCT, MDCT angiography, EUS-FNA, PET/CT, MRI) when used to diagnose and/or stage pancreatic adenocarcinoma?
 - a. How are patient factors related to the harms of different imaging techniques?
 - b. What are patient perspectives on the tolerance of different imaging techniques and the balance of benefits and harms of different imaging techniques?

4. What is the screening accuracy of imaging techniques (e.g., MDCT, MDCT angiography, EUS-FNA, PET/CT, MRI) for detecting precursor lesion(s) of pancreatic cancer or pancreatic adenocarcinoma in high-risk asymptomatic adults (i.e., those at genetic or familial risk of pancreatic adenocarcinoma)?

PICOTS

Populations

- Adult patients with symptoms in whom pancreatic adenocarcinoma is suspected
- Adult patients with symptoms with an established diagnosis of pancreatic adenocarcinoma
- Adult patients without symptoms who are at high risk of having or developing pancreatic adenocarcinoma (family history or genetic risk factor)

Interventions

Imaging using one or more of the following tests:

- Multidetector computed tomography (MDCT)
- MDCT angiography (with or without 3D reconstruction)
- Endoscopic ultrasound with fine-needle aspiration (EUS-FNA)
- Magnetic resonance imaging (MRI)
- Positron emission tomography combined with computed tomography (PET/CT)

Comparators

- Any direct comparisons of the imaging tests of interest
- Reference standards to assess test performance
 - Histopathological examination of tissue and/or biopsy
 - Intra-operative findings
 - Clinical followup

Outcomes

- Accuracy
 - Test performance (sensitivity, specificity, under-, overstaging)
- Intermediate outcomes
 - Therapeutic management
- Clinical outcomes
 - Mortality
 - Quality of life
- Adverse effects and harms
 - Procedural harms of testing (e.g., radiation exposure, puncture from FNA)

Timing

- Any time points will be considered

Setting

- Any setting will be considered

Methods

Search Strategy

Medical Librarians in the Evidence-based Practice Center (EPC) Information Center performed literature searches, following established systematic review protocols. We searched the following databases using controlled vocabulary and text words: Embase, MEDLINE, PubMed, and The Cochrane Library from 1980 through November 1, 2013. The literature searches will be updated during the peer review process, before finalization of the review.

Study Selection

Our criteria are listed in five categories below: (1) publication criteria, (2) study design criteria, (3) patient criteria, (4) test criteria, and (5) data criteria.

Publication Criteria

- a. Full-length articles: The article must have been published as a full-length, peer-reviewed study.
- b. Redundancy: To avoid double-counting patients, in instances in which several reports of the same or overlapping groups of patients were available, only outcome data based on the larger number of patients were included. However, we included data from publications with lower numbers of patients when either (a) a publication with lower patient enrollment reported an included outcome that was not reported by other publications of that study, or (b) a publication with lower patient enrollment reported longer followup data for an outcome.
- c. English language: Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translating studies.
- d. Publication date: We included studies published since January 1, 2000. Older articles likely included outdated technologies. Studies of harms of imaging technologies that did not specifically involve pancreatic adenocarcinoma (i.e., any clinical indication), must have been published since January 1, 2009.

Study Design Criteria

- a. For KQs on single-test accuracy: For KQs 1a and 1b, which address the performance of a single imaging test against a reference standard, we included only systematic reviews. EPC guidance by White et al. (2009)¹² states how existing systematic reviews can be used to replace de novo processes in comparative effectiveness reviews. We referred to the PICOTS-SD for the pertinent subquestion, and these seven components (Populations, Interventions, Comparisons, Outcomes, Time points, Setting, Study design) were the seven inclusion criteria. For quality, see section on risk of bias.
- b. For any KQs comparing two or more tests, the study must have compared both tests to a reference standard. The reference standard must not have been defined by either imaging test being assessed.

- c. For any KQs on single versus multiple tests, test experience, patient factors (e.g., age), or tumor characteristics (e.g., head or tail of pancreas), the study must have made a comparison of data to address the question.
- d. For any KQs involving comparative clinical management or long-term survival/quality of life, some patients must have received one of the imaging tests, and a separate group of patients must have received a different imaging test. This design permits a comparison of how the choice of test may influence management and/or survival and/or quality of life.
- e. For KQ3 on the rates of procedural harms, we included any reported harms data based on 50 or more patients, in the context of diagnosis or staging of pancreatic adenocarcinoma, on the harms of imaging procedures that contained a statement in the Methods section that the study planned in advance to capture harms/complications data. Additionally, we included studies primarily of harms and adverse events associated with the use of each specific imaging modality, regardless of the type of cancer being detected, that were published in 2009 or later.
- f. For KQ3b on patient perspectives of imaging tests, any study design was accepted.
- g. For KQ4 on screening, we included any study that reported the performance of at least one included imaging test in the context of screening for either pancreatic adenocarcinoma itself or precursor lesions to pancreatic cancer.

Patient Criteria

- a. To be included, the study must have reported data obtained from groups of patients in which at least 85 percent of the patients were from one of the patient populations of interest. If a study reported multiple populations, it must have reported data separately for one or more of the populations of interest.
- b. Adults. At least 85 percent of patients must have been aged 18 years or older, or data must have been reported separately for those aged 18 years or older.
- c. Studies of the screening/diagnosis/staging of *primary* pancreatic adenocarcinoma were included. Testing for *recurrent* pancreatic cancer was excluded.
- d. Data on imaging tests performed after any form of treatment (e.g., neoadjuvant chemotherapy) were excluded, but pretreatment imaging data were considered.

Test Criteria

- a. Type of test. Only studies of the imaging tests of interest were included (listed in the key questions above). Studies of computed tomography (CT) that did not explicitly state that (or it could not be determined that) CT was MDCT were assumed to be MDCT. Given our publication date criterion of 2000 and later, we believe it is safe to assume that CT performed in such studies was MDCT.

Data Criteria

- a. The study must have reported data pertaining to one of the outcomes of interest (see the key questions section).

- For accuracy outcomes (KQ1a through 1e, KQ2a through 2e, and KQ4), this means reporting enough information for one to calculate both sensitivity and specificity, along with corresponding confidence intervals (CIs).
 - For clinical management (KQ1f, KQ2f), this means reporting the percentage of patients who received a specific management strategy, after undergoing each imaging test (a separate group of patients corresponding to each imaging test).
 - For long-term survival (KQ1g, KQ2g), this means either reporting median survival after each imaging test (separate groups of patients), or mortality rates at a given time point (separate groups of patients), or other patient survival such as a hazard ratio.
 - For quality of life (KQ1g, KQ2g), this means reporting data on a previously validated quality-of-life instrument (such as the SF-36) after each imaging test (separate groups of patients).
 - For harms (KQ3), this means a statement appearing in the Methods section that harms/complications would be measured, reporting the occurrence of a procedure-related harm and number of patients at risk, or the reporting that no harms or complications occurred as a result of the procedure.
 - For patient perspectives (KQ3b), this means reporting the results of asking patients about their opinions or experience after having undergone one or more of the imaging tests.
- b. Regarding the minimum patient enrollment, for studies comparing imaging tests (KQ1b through 1g; KQ2b through 2g), we required data on at least 10 patients per imaging test. We also used a minimum of 10 for KQ3b on patient perspectives of imaging tests. We used a minimum of 50 patients for data on harms (KQ3) or screening (KQ4).
 - c. For all KQs, the reported data must have included at least 50 percent of the patients who had initially enrolled in the study.
 - d. Studies that reported data by tumor (e.g., *x* percent of pancreatic adenocarcinoma *tumors* were correctly detected) instead of by patient (e.g., *x* percent of enrolled *patients* were correctly given a diagnosis of pancreatic adenocarcinoma) were not excluded because of this difference. However, we separated the tumor-based data from the patient-based data because they measure different types of accuracy.

Data Abstraction

Duplicate abstraction of comparative accuracy data was used to ensure accuracy. All discrepancies were resolved by consensus discussion. Elements abstracted included general study characteristics (e.g., country, setting, study design, number of subjects enrolled), patient characteristics (e.g., age, sex, comorbidities), details of the imaging methodology (e.g., radiotracer, timing of test), risk-of-bias items, and outcome data.

Risk of Bias Evaluation

For systematic reviews of single-test accuracy, we used a revised AMSTAR (Assessment of Multiple Systematic Reviews) instrument. For each included review, two analysts independently answered 15 items on the AMSTAR instrument and independently assessed the systematic

review as either high quality or not high quality. Discrepancies in the category assignment were resolved by consensus. For primary studies comparing two or more tests, we used a set of nine risk-of-bias items after considering the QUADAS-2,¹³ as well as additional issues that specifically address bias in the comparison of diagnostic tests.

Data Analysis and Synthesis

For comparing imaging tests, we synthesized the evidence using meta-analysis wherever appropriate and possible. When meta-analysis was not possible (because of clinical heterogeneity or limitations of reported data) or was judged to be inappropriate, the data were synthesized using a descriptive narrative review approach.

For each pair of imaging tests compared directly by a group of studies (e.g., MDCT and EUS-FNA) for a given clinical purpose (e.g., diagnosis), we performed bivariate meta-analysis¹⁴ of each test's accuracy data using the "metandi" command in STATA,¹⁵ or separate analyses of sensitivity and specificity using Meta-Disc.¹⁶ Using the meta-analytic results, we used equation 39 in Trikalinos et al. (2013)¹⁷ to compare the tests statistically (separately for sensitivity and specificity). For statistical tests, we set $p=0.05$ two-tailed as the threshold for statistical significance. If a comparison was not statistically significant, two reviewers independently judged whether the CI around the difference was sufficiently narrow to permit a conclusion of similar accuracy; disagreements were resolved by consensus.

Strength of Evidence Grading

We used the EPC system for grading evidence on diagnostic tests as described in the EPC guidance chapter by Singh et al. (2012).¹⁸ This system uses up to eight domains as inputs (study limitations, directness, consistency, precision, reporting bias, dose-response association, all plausible confounders would reduce the effect, strength of association). Reporting bias was addressed by considering unpublished trials listed in clinicaltrials.gov as well as trial funding sources. The output is a grade of the strength of evidence: high, moderate, low, or insufficient. This grade is made separately for each outcome of each comparison of each KQ. The grades are defined as follows:

- High: We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable—that is, another study would not change the conclusions
- Moderate: We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient. We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

We selected the most important outcomes to be graded. For this report, we graded evidence on comparative accuracy for diagnosis, resectability in patients with unstaged disease, staging (including its components T [tumor] staging, N [nodal] staging, metastases, vessel involvement,

and precise stage), resectability in patients whose disease has been staged, and clinical outcomes (clinical management, survival, and quality of life). These were the most important outcomes, and the EPC guidance chapter by Singh et al. (2012)¹⁸ can be applied. We did not grade the strength of evidence from published systematic reviews on the accuracy of individual imaging tests, or the procedural harms of a single imaging test, or screening accuracy.

For each comparison and each outcome, we determined whether the evidence permitted an evidence-based conclusion. For comparative test accuracy, this meant determining whether the evidence was sufficient to permit one of the following three types of conclusions: (1) test A is more accurate than test B, (2) test B is more accurate than test A, or (3) tests A and B are similarly accurate. The first two types of conclusions required a statistically significant difference for either sensitivity or specificity (or both), whereas the third type of conclusion required a nonstatistically significant difference for both sensitivity and specificity, as well as independent judgments from two reviewers that the data were precise enough to indicate similar accuracy. If none of these three conclusions were appropriate, we graded the evidence insufficient. If the evidence was sufficient to permit a conclusion, then the grade was high, moderate, or low. The grade was provided by two independent raters, and discrepancies were resolved by consensus. When the evidence base consisted of a single study, the evidence was considered insufficient unless the study had all of the following characteristics: low risk of bias, the evidence was direct, there was nothing that raised concern about reporting bias, the finding was precise, and one of the three types of conclusions described above could be drawn.

Applicability

The applicability of the evidence involves four key aspects: patients, tests/interventions, comparisons, and settings.¹⁹ In considering the applicability of the findings to patients, we consulted large studies to ascertain the typical characteristics of patients newly given a diagnosis of pancreatic adenocarcinoma (e.g., age, sex) and then to assess whether the included studies enrolled similar patients. Some aspects of interventions may also affect applicability, for example, if a study uses an uncommonly used radiotracer. Settings of care were to be described, and if data permitted, subgroups of studies by setting were analyzed separately.

Peer Review and Publication

Peer reviewers were invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report were considered by the EPC in preparation of the final draft of the report. The dispositions of the peer review comments are documented and will be published 3 months after the publication of the evidence report.

Results

Evidence Base

The literature searches identified 9,776 citations, and after duplicate review, we excluded 9,036 of them. The most common reason for exclusion was that the article did not involve diagnosis, staging, screening, or harms. We retrieved the other 740 articles, and after duplicate review, we excluded 610 of those. The most common reason was that the study reported data only on a single imaging test of interest and did not meet inclusion criteria for other KQs. See

Appendix B for a list of the publications excluded at the full article level. We included the remaining 130 publications, which described 123 unique studies/reviews (seven publications reported overlapping patients). Of the 123, 15 were systematic reviews and 108 were primary studies.

KQ1: Comparative Effectiveness of Imaging Techniques for Diagnosis

KQ1a. What is the accuracy of each imaging technique for diagnosis and assessment of resectability?

Thirteen systematic reviews met the inclusion criteria for this question, of which four were both recent (published 2009 or later) and of high quality (meeting all eight of the quality criteria on the revised AMSTAR instrument deemed most important). We did not grade the strength of the evidence from systematic reviews.

For EUS-FNA in diagnosing pancreatic cancer, we included eight reviews, and four were recent and high-quality. The four recent high-quality reviews reported summary sensitivity results ranging from 85 percent to 93 percent and summary specificity results ranging from 94 percent to 100 percent. CT was addressed in only one review, which was deemed not of high quality and is now outdated (2005). MRI was addressed in three reviews, none of which were high quality. The reviews agreed on MRI sensitivity, with meta-analysis results ranging from 84 percent to 86 percent, but differed on specificity, with the two reviews from one group reporting 91 percent specificity and the other review reporting 82 percent. PET/CT was addressed in three reviews, none of which were high quality.

The only review that included resectability as an outcome was outdated, of low quality, and analyzed only CT and MRI studies. For CT, the study estimated sensitivity at 81 percent and specificity at 82 percent; for MRI, the study estimated sensitivity at 82 percent and specificity at 78 percent.

The limitations of the evidence for KQ1a involve limitations of the available systematic reviews. A de novo analysis of single test diagnostic accuracy studies (which was outside the scope of this report) could may permit more estimates of single test diagnostic accuracy.

KQ1b. What is the comparative accuracy of the different imaging techniques for diagnosis and assessment of resectability?

Eighteen included studies addressed this question. For diagnostic accuracy, three studies compared MDCT with EUS-FNA, seven studies compared MDCT with MRI, six studies compared MDCT with PET/CT, one study compared EUS-FNA with PET/CT, and one study compared MRI with PET/CT. For resectability in patients with unstaged disease, one study compared MDCT angiography with 3D reconstruction to MDCT angiography without 3D reconstruction, one study compared MDCT with EUS-FNA, and two studies compared MDCT with MRI. All studies had a low or moderate risk of bias.

In most cases, the combined evidence indicated neither a difference nor equivalence between two imaging technologies. The imprecision, therefore, often prevented any conclusions about comparative accuracy. For two cases, however, the evidence was sufficient to permit conclusions. One involved the comparison between MDCT and EUS-FNA with respect to the accuracy of resectability assessment in patients with unstaged disease. Based on one study, we found similar accuracy between the two modalities, with sensitivities of 64 percent to 68 percent and specificities of 88 percent to 92 percent. Another conclusion involved the comparison

between MDCT and MRI with respect to diagnostic accuracy, which was performed in seven studies. These studies found consistently high sensitivity (89%) and specificity (90%) for both imaging modalities.

There were no included studies reporting pertinent data for all other subquestions for KQ1.

Conclusions for KQ1

Thirteen included systematic reviews yielded the following conclusions regarding single-test accuracy for diagnosis and assessment of resectability in unstaged patients:

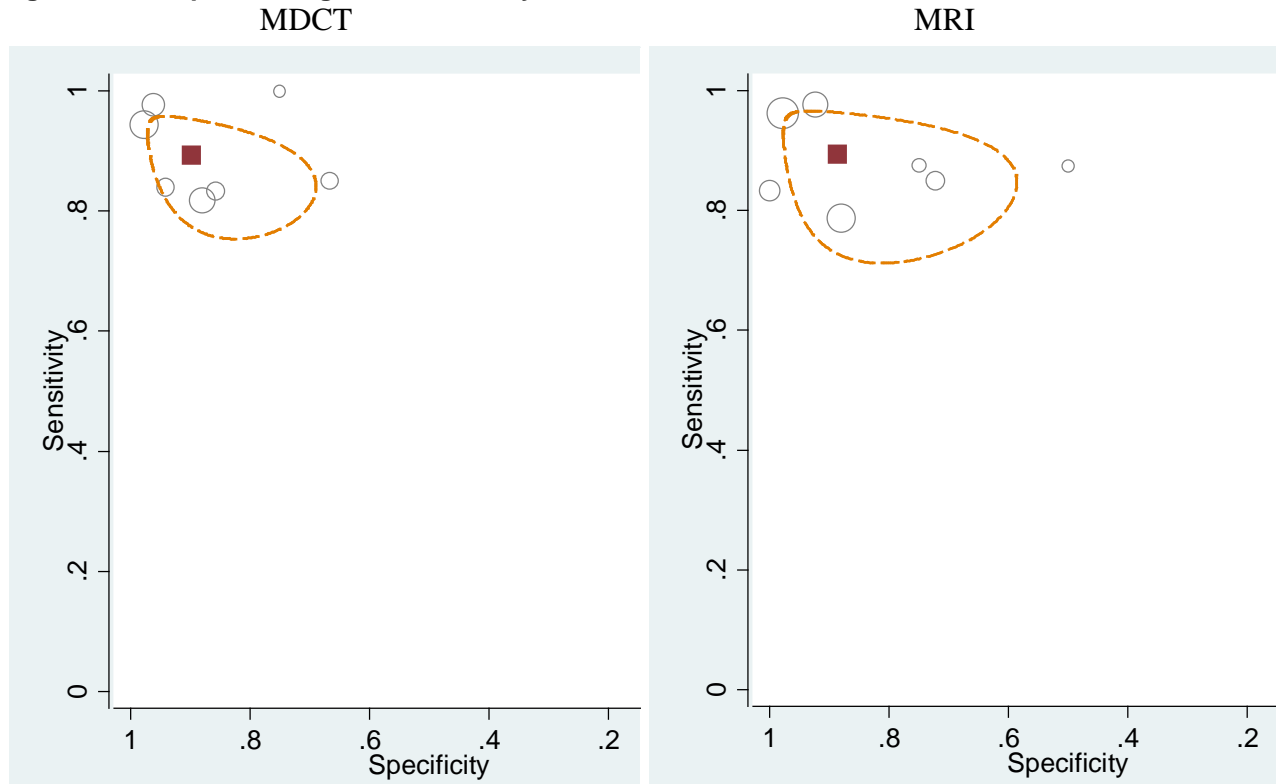
- Evidence was insufficient to permit accuracy estimates for MDCT angiography with or without 3D reconstruction.
- For diagnosis using MDCT, one systematic review yielded a sensitivity estimate of 91 percent (95% CI, 86% to 94%) and a specificity estimate of 85 percent (95% CI, 76% to 91%). (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using EUS-FNA, four high-quality and recent systematic reviews yielded sensitivity estimates ranging from 85 percent to 93 percent and specificity estimates ranging from 94 percent to 100 percent. (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using MRI, three systematic reviews yielded sensitivity estimates of 84 percent to 86 percent and specificity estimates of 82 percent to 91 percent.²⁰⁻²² (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using PET/CT, three systematic reviews yielded sensitivity estimates of 87 percent to 90 percent and specificity estimates of 80 percent to 85 percent.^{20,23,24} (Strength of evidence from published systematic reviews was not graded.)
- For MDCT, in assessing the resectability of tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 81 percent (95% CI, 76% to 85 percent) and a specificity estimate of 82 percent (95% CI, 77 percent to 97%). (Strength of evidence from published systematic reviews was not graded.)
- For MRI, in assessing the resectability of tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 82 percent (95% CI, 69% to 91%) and a specificity estimate of 78 percent (95% CI, 63% to 87%).²² (Strength of evidence from published systematic reviews was not graded.)

For comparative diagnostic accuracy and resectability in unstaged patients, we included 18 primary studies, and drew the following conclusions:

- Based on one study, MDCT and EUS-FNA have similar accuracy in the assessment of resectability of pancreatic adenocarcinoma in symptomatic adults with unstaged disease (Strength of evidence: low). Based on the study's prevalence of 53 percent, the results mean that those whose disease is deemed unresectable by either MDCT or EUS-FNA have about an 88 percent chance of their disease actually being unresectable, and those whose disease is deemed resectable by either test have about a 70 percent chance of their disease actually being resectable.
- Based on seven studies, MDCT and MRI have similar accuracy in the diagnosis of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate). A figure of the meta-analysis appears in Figure A below. Based on the mean prevalence of 53 percent, the results mean that a patient with a positive test result (on

either MDCT or MRI) has approximately a 90 percent chance of having pancreatic adenocarcinoma, whereas a patient with a negative test result (on either MDCT or MRI) has only a 12 percent chance of having pancreatic adenocarcinoma.
No included studies addressed KQ1c-g, thus we drew no conclusions about those issues.

Figure A. ROC plot of diagnostic accuracy, MDCT versus MRI



The left side of the plot shows the multidetector computed tomography (MDCT) data in receiver operating characteristic (ROC) space; the right side shows the magnetic resonance imaging (MRI) data in ROC space. Each study contributed one circle to each side of the plot. The filled square shows the summary estimate, and the dashed region shows the 95% confidence interval range around the summary estimate.

For comparative test accuracy for KQ1, our strength of evidence assessments appear in Table A.

Table A. Summary of evidence on comparative accuracy for KQ1

Comparison and Clinical Decisions	# Studies, # Patients, and Overall Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence	Conclusion
MDCT angiography without 3D reconstruction vs. with 3D reconstruction; resectability in those with unstaged disease	1 Total N=57 Low	Direct	Unknown	Precise	Yes*	Insufficient	NA
MDCT vs. EUS-FNA, diagnosis	3 Total N=302 Medium	Direct	Inconsistent	Imprecise	No	Insufficient	NA
MDCT vs. EUS-FNA; resectability in those not staged	1 Total N=53 Low	Direct	Unknown	Precise	No	Low	Similar accuracy
MDCT vs. MRI, diagnosis	7 Total N=397 Medium	Direct	Consistent	Precise	No	Moderate	Similar accuracy
MDCT vs. MRI; resectability in those not staged	2 Total N=79 Low	Direct	Consistent	Imprecise	No	Insufficient	NA
MDCT vs. PET/CT, diagnosis	6 Total N=278 Medium	Direct	Consistent	Imprecise	No	Insufficient	NA
EUS-FNA vs. PET/CT, diagnosis	1 Total N=45 Medium	Direct	Unknown	Imprecise	No	Insufficient	NA
MRI vs. PET/CT, diagnosis	1 Total N=38 Medium	Direct	Unknown	Imprecise	No	Insufficient	NA

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; NA = not applicable; PET/CT = positron emission tomography–computed tomography.

Note: In addition to considering study limitations and the domains of directness, consistency, precision and reporting bias, we considered whether a conclusion could be drawn about difference or equivalence in determining the strength of evidence.

*Possible reporting bias in the single study involving MDCT angiography because the study was performed by the developers of the 3D reconstruction software under consideration.

KQ2: Comparative Effectiveness of Imaging Techniques for Staging

KQ2a. What is the staging accuracy of each imaging technique (for tumor size, lymph node status, vessel involvement, metastases, stage I–IV, and resectability)?

Three systematic reviews were included for this question. There were two reviews for the diagnosis of vascular invasion: both included CT results and one also reviewed MRI data. One review analyzed both the full set of CT studies and a subset of studies using multi-slice scanners. Sensitivity was considerably higher for the more recent studies than for the older ones (Evidence Table C-6), with no corresponding loss of specificity. A review of MRI found only four studies and thus had a large uncertainty in its results. A review of PET for pancreatic cancer staging also tabulated a subset of studies using integrated PET/CT scanners. It found only one such study, which reported on only 50 patients.

As with KQ1a, the limitations of the evidence for KQ2a involve limitations of the available systematic reviews. A de novo analysis of single test staging accuracy studies (which was outside the scope of this report) may permit more estimates of single test staging accuracy.

KQ2b. What is the comparative staging accuracy of the different imaging techniques?

Twelve included studies (low or moderate risk of bias) addressed this question. For the accuracy of the assessment of metastases, five studies compared MDCT with MRI, and two compared MDCT and PET/CT. Three studies also compared MDCT and MRI with respect to the assessment of vessel involvement. All other test comparisons and aspects of staging were analyzed by no more than one study apiece.

In most cases, the combined evidence indicated neither a difference nor equivalence between two imaging technologies. The imprecision, therefore, often prevented any conclusions about comparative accuracy. For three cases, however, the evidence was sufficient to permit conclusions. One conclusion, based on one study, involved the superiority in T-stage accuracy of EUS-FNA over MDCT (~67% of cases were accurately T-staged by EUS-FNA as compared with only 41% by MDCT; this was due to a lower rate of undersizing the tumor by EUS-FNA). Another conclusion, based on three studies, was the similarity in the accuracy of the assessment of vessel involvement by MDCT and MRI (sensitivities of 62% to 68%, specificities of 96% to 97%). The third conclusion, based on two studies, was that PET/CT is more accurate in assessing distant metastases than MDCT (67% vs. 57% for sensitivity, and 100% vs. 91% for specificity).

No included studies addressed KQ2c-g, thus we drew no conclusions about those issues.

Conclusions for KQ2

Three included systematic reviews yielded the following conclusion about single-test accuracy of imaging tests for staging and tumor resectability in patients whose disease is staged:

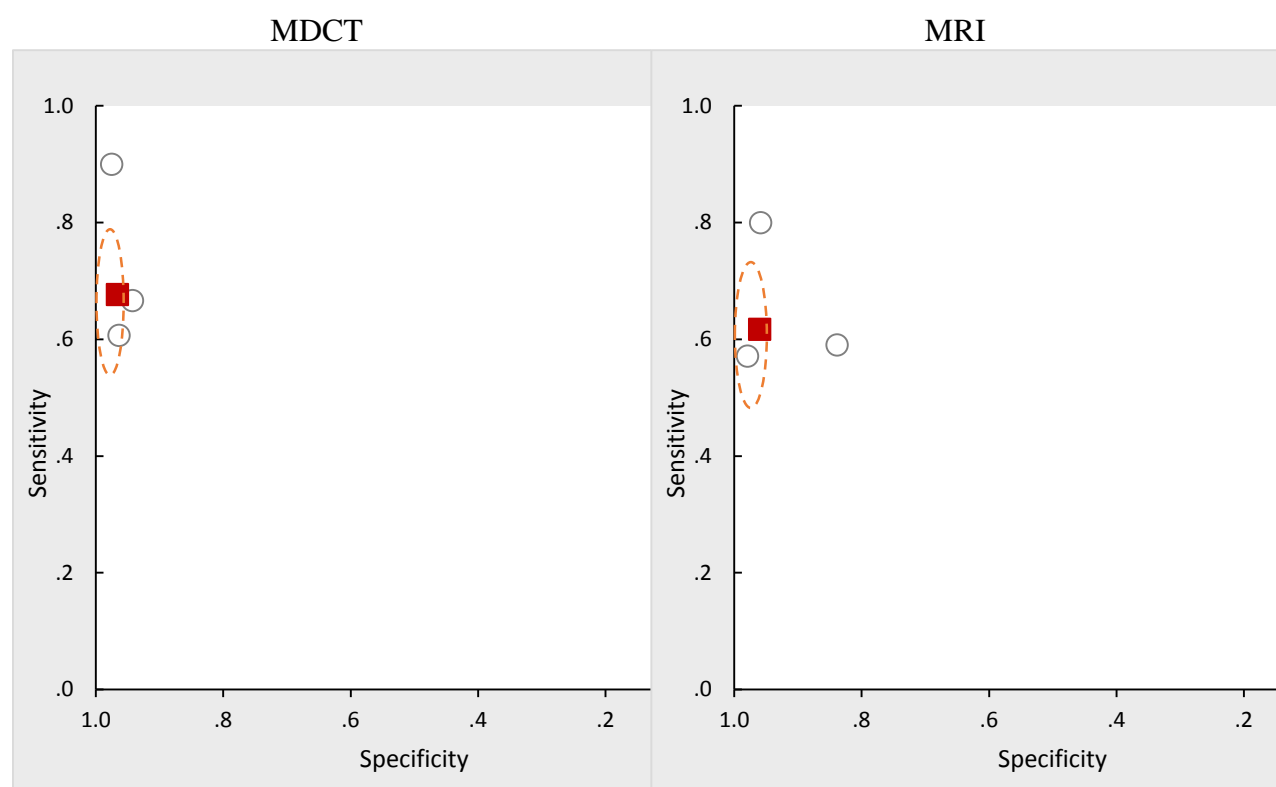
- Two systematic reviews that were not high quality reported on CT for assessing vascular invasion. Both concluded that sensitivity and specificity were worse for the subset of studies using older or single-slice CT scanners than for the studies using newer multi-slice CT. Summary sensitivity values for the newer scanners ranged from 80 percent to 85 percent while summary specificity ranged from 82 percent to 97 percent. The evidence base in both reviews was small: four or five studies each.
- One low-quality systematic review reported on MR for assessing vascular invasion, concluding it had sensitivity of 63 percent and specificity of 93 percent. The evidence base was only four studies.
- One review of PET/CT included only a single study, which had reported 82 percent sensitivity and 97 percent specificity for detecting liver metastasis.

For comparative staging accuracy, we included a total of 12 primary studies, and we drew the following conclusions:

- Based on one study, EUS-FNA is more accurate than MDCT in assessing the T stage of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: low)
- Based on three studies, MDCT and MRI have similar accuracy in assessing the vessel involvement of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate). A figure of the meta-analysis appears in Figure B.
- Based on two studies, PET/CT is more accurate than MDCT in assessing distant metastases of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: low). A figure of the meta-analysis appears in Figure C.

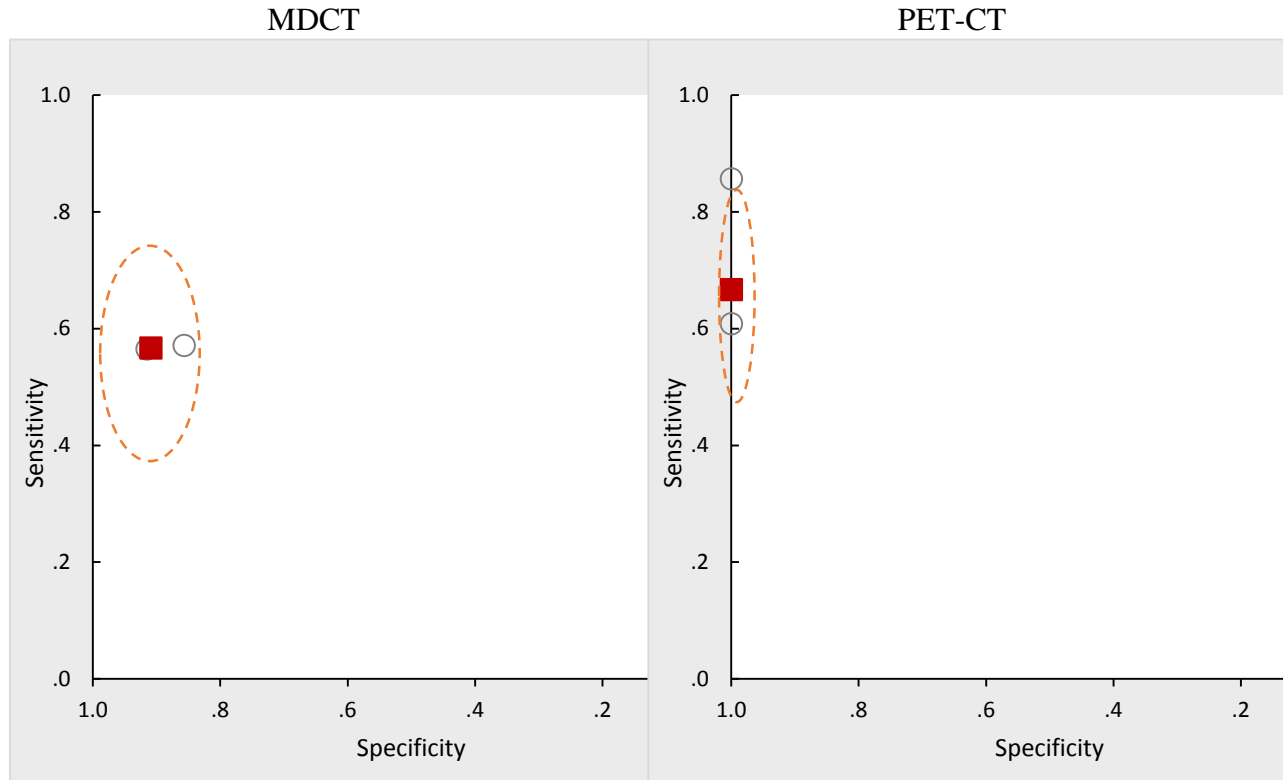
No included studies addressed KQ2c-g, thus we drew no conclusions about those issues.

Figure B. ROC plot of vessel involvement, MDCT versus MRI



The left side of the plot shows the multidetector computed tomography (MDCT) data in receiver operating characteristic (ROC) space; the right side shows the magnetic resonance imaging (MRI) data in ROC space. Each study contributed one circle to each side of the plot. The filled square shows the summary estimate, and the dashed region shows the 95% confidence interval range around the summary estimate.

Figure C. ROC plot of metastases, MDCT versus PET-CT



The left side of the plot shows the multidetector computed tomography (MDCT) data in receiver operating characteristic (ROC) space; the right side shows the positron emission tomography–computed tomography (PET-CT) data in ROC space. Each study contributed one circle to each side of the plot. The filled square shows the summary estimate, and the dashed region shows the 95% confidence interval range around the summary estimate.

For comparative test accuracy for KQ2, our strength-of-evidence assessments appear in Table B below.

Table B. Summary of evidence on comparative accuracy for KQ2

Comparison and Staging Judgment	# Studies and Overall Study Limitations	Directness	Consistency	Precision	Report- ing Bias	Strength of Evidence	Conclusion
MDCT vs. EUS-FNA, T staging	1 Total N=49 Low	Direct	Unknown	Precise	No	Low	Evidence favors EUS-FNA
MDCT vs. EUS-FNA, vessel involvement	1 Total N=50 Medium	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI, T staging	1 Total N=59 Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI, N staging	1 Total N=58 Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI, Metastases	5 Total N=232 Low	Direct	Inconsistent	Imprecise	No	Insufficient	NA
MDCT vs. MRI, precise stage	1 Total N=59 Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI, vessel involvement	3 Total N=213 Low	Direct	Consistent	Imprecise	No	Moderate	Similar accuracy
MDCT vs. MRI; resectability in those staged	1 Total N=59 Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. PET/CT, N staging	1 Total N=47 Medium	Direct	Unknown	Precise	No	Insufficient	NA
MDCT vs. PET/CT, metastases	2 Total N=96 Medium	Direct	Consistent	Precise	No	Low*	Evidence favors PET/CT
EUS-FNA vs. MRI, precise stage	1 Total N=48 Medium	Direct	Unknown	Precise	No	Insufficient	NA
MRI vs. PET/CT, metastases	1 Total N=14 Low	Direct	Unknown	Imprecise	No	Insufficient	NA

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration; M = metastasis; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; N = nodal; NA = not applicable; PET/CT = positron emission tomography-computed tomography; T = tumor.

Note: In addition to considering study limitations and the domains of directness, consistency, precision and reporting bias, we considered whether a conclusion could be drawn about difference or equivalence in determining the strength of evidence.

*We graded the evidence as Low due to medium risk of bias, the fact that there were only two studies, and the advantage of PET-CT over MDCT was statistically significant for specificity but not for sensitivity.

KQ3: Harms of Imaging Techniques for Diagnosis and/or Staging

We included a total of 78 studies for this KQ: 50 described harms due to imaging tests for the diagnosis/staging of pancreatic cancer and were published in the year 2000 or later, and the other 28 were not specific to pancreatic cancer and were published in the year 2009 or later. The large majority of pancreas-specific studies reported the procedural harms of EUS-FNA. The most commonly reported harms in such studies were pancreatitis (occurring in 0% to 3.7% of patients), postprocedural pain (occurring in 0.1% to 2.0% of patients), and bleeding/puncture/perforation (occurring in 0% to 4.3% of patients).

KQ3a. How are patient factors related to the harms of different imaging techniques?

No included studies addressed this question.

KQ3b. What are patient perspectives on the tolerance of different imaging techniques and the balance of benefits and harms of different imaging techniques?

One included study found that about 10 percent of patients state that EUS-FNA is very uncomfortable, and 11 percent of patients state that MRI is very uncomfortable. For EUS-FNA, the stated reason for lack of comfort involved either inadequate sedation or oversedation, whereas for MRI the stated reason involved claustrophobia.

Conclusions for KQ3

In the diagnosis and staging of pancreatic adenocarcinoma, different imaging tests are associated with different types of harms. We did not grade the strength of evidence for harms.

- MDCT and PET/CT use radiation and therefore can cause cancer, but the size of the risk is not possible to estimate specifically when used for diagnosis/staging of pancreatic adenocarcinoma.
- EUS-FNA risks are due to the physical invasiveness of the procedure and primarily involve pancreatitis, postprocedural pain, and puncture, perforation, and bleeding.
- MRI risks mainly involve adverse reactions to contrast media.
- Regarding patient tolerance, one study of screening found that about 10 percent of patients stated that EUS-FNA and MRI are very uncomfortable.

KQ4: Imaging Techniques for Screening Asymptomatic People

We included a total of six studies for this KQ, five of which were published in the year 2009 or later. The group of studies was heterogeneous in the populations studied, imaging tests examined, the design of study, and reporting of results, which limits generation of conclusions. Studies defined high-risk individuals (HRIs) differently, with most based on a combination of personal and family history of pancreatic cancer and/or a familial cancer syndrome (i.e., familial pancreatic cancer) and/or a hereditary predisposition to tumors (i.e., Peutz-Jeghers syndrome). One study had a control arm of non-HRIs, however, we examined only the data on HRIs. Two studies looked at one-time-only initial screening of HRIs, whereas four studies had followup screening annually or more frequently for individuals for whom it was indicated. Followup times ranged from 5 to 50.4 months.

One study examined the use of MRI only for screening HRIs, whereas the others looked at a combination of MRI/magnetic resonance cholangiopancreatography (MRCP) with EUS with or without FNA, some with the addition of MDCT and endoscopic retrograde cholangiopancreatography. Most of these studies were not designed to assess accuracy of individual imaging modalities for screening HRIs, but rather the accuracy of screening HRIs with a combination of imaging modalities as deemed clinically appropriate. Similarly, they were not designed to assess comparative accuracy of imaging modalities. Therefore, studies did not uniformly or comprehensively report results for each imaging modality performed, which prevents conclusions about accuracy of any particular imaging tests or comparative accuracy.

Conclusions for KQ4

Six included studies involved screening high-risk asymptomatic adults for detecting precursor lesion(s) of pancreatic cancer or pancreatic adenocarcinoma.

- No accuracy estimates are possible for any single imaging modality, because the six included screening studies provided accuracy data only for a joint set of imaging tests.
- Two percent to 18 percent of HRIs screened received either a biopsy or surgery based on imaging findings on any imaging modality— MDCT, EUS-FNA, or MRI— amounting to a total of 43 of 665 HRIs (7%) from all six studies.
- Of 46 patients with a pathological specimen from either biopsy or surgery in the six screening studies, 17 total (1.1% to 9.0% of HRIs screened) had true-positive findings (i.e., pathology-confirmed precursor lesions or pancreatic adenocarcinoma); 19 total (0% to 9.8% of HRIs screened) had major false-positive findings (i.e., patient had surgical resection based on imaging and pathology that showed a benign lesion, e.g., branch duct intraductal papillary mucinous neoplasia [BD-IPMN] with low-grade dysplasia); seven total (0% to 9.2% of HRIs screened) had a minor false-positive finding (i.e., patient had a FNA biopsy based on imaging but pathology was normal, so no surgery was performed). An additional three patients (0% to 1.5% of HRIs screened) had false-negative findings (i.e., patient's cancer was missed on image screening but found on later screening with pathology confirmation).

Discussion

Key Findings and Strength of Evidence

This comparative review summarizes evidence on imaging tests (MDCT, MRCP, EUS-FNA, MRI, and PET/CT) for pancreatic adenocarcinoma with respect to four areas: diagnosis, staging, harms, and screening. Diagnostic and staging accuracy are reasonable for several tests, but direct comparative evidence was generally not precise enough to demonstrate clear advantages of one test over another or to demonstrate similar accuracy among tests. We conclude that MDCT and EUS-FNA have similar accuracy in assessing resectability of tumors in patients with unstaged disease and that EUS-FNA is less likely to undersize tumors than MDCT with respect to T staging. Further, we conclude that MDCT and MRI are similarly accurate with respect to both diagnosis and assessment of vessel involvement. For PET/CT, evidence was generally inconclusive, but we found sufficient evidence to conclude that PET/CT

is more accurate in assessing distant metastases than MDCT (67% vs. 57% for sensitivity, and 100% vs. 91% for specificity).

Regarding the procedural harms of imaging tests in the diagnosis and staging of pancreatic adenocarcinoma, the harms of concern are different for different tests. MDCT and PET/CT use radiation and, therefore, could theoretically increase the risk of developing cancer over time. However, the size of the risk is not possible to estimate, specifically when used for diagnosis and staging of pancreatic adenocarcinoma. Furthermore data on the importance of this risk relative to the data obtained from these tests is unknown. EUS-FNA risks are due to the physical invasiveness of this procedure and primarily involve pancreatitis, postprocedural pain, and puncture, perforation, and bleeding. Regarding patient tolerance, one study of screening found that about 10 percent of patients state that EUS-FNA and MRI are very uncomfortable.

One of the practical challenges of this review is that while our KQs looked separately at the comparative effectiveness of imaging procedures for diagnosis, staging, and resectability, generally speaking these determinations occur simultaneously or in rapid succession. So, the question naturally arises, do our findings mean that all four imaging modalities should be used in the evaluation of patient's with suspected pancreatic adenocarcinoma? Specifically, should an individual have an MDCT or MRI for diagnosis, assessment of vessel involvement, and potential resectability determination, followed by an EUS-FNA for tumor staging, followed by a PET/CT for metastatic staging? Although our results did not permit determination of the optimal sequencing of imaging tests, they suggest that MDCT or MRI, plus EUS-FNA, plus PET/CT may all be appropriate for the diagnosing, staging, and resectability determination of suspected pancreatic adenocarcinoma. However, it should be noted that these four imaging studies are not equally available at all institutions, and each study has its associated risks of harms as well as patient preferences and tolerances.

Existing practice follows a multi-modality paradigm for diagnosis and staging of pancreatic cancer that is largely institution-specific based on technology and resource availability and institution and provider preference, an approach that allows for potential inappropriate variation and disparities in care. This report sheds additional light on which imaging modalities are more accurate or roughly equivalent for some aspects of diagnosis and staging of pancreatic adenocarcinoma, and could be incorporated into additional guidance developed for clinicians.

When screening individuals at high risk of developing pancreatic adenocarcinoma, 2 percent to 18 percent of HRIs screened, by any imaging modality (MDCT, EUS-FNA, MRI) had a result that warranted either a biopsy or surgery based on imaging findings. Available studies do not report results for individual imaging modalities, therefore, one cannot determine the screening accuracy of any given imaging test. At this time, further research is needed to elucidate the preferred imaging modalities (and other tests) for screening HRIs.

Applicability

The applicability of the existing evidence to current practice is mixed:

- Regarding patients, the typical age of patients in the included studies was 60–65 years, which is slightly younger than the median age at diagnosis of pancreatic cancer (71 years). Resection may be more appropriate for younger patients (because of fewer comorbidities), but the comparative accuracy of different tests (e.g., MDCT vs. EUS-FNA) may not vary by age. The gender ratio in the included studies was representative (slightly fewer than half the patients were women).

- Regarding tests and comparisons, we attempted to ensure applicability by including only studies of imaging technologies that are currently in wide use for the diagnosis and staging of pancreatic adenocarcinoma. Specific test protocols, however, may differ between the studies we included and the typical test parameters used outside the context of a research study.
- Regarding settings, academic settings were overrepresented in the evidence we reviewed. The implication of this is unclear, but the test readers or practitioners in these publications may be more experienced than at nonacademic centers.

Research Gaps

We identified four important gaps. The first important gap concerns the general lack of specific evidence on MDCT angiography, which is a newer technology that has not been sufficiently studied.

The second important gap concerns the lack of evidence on comparative longer-term outcomes such as how patients were managed differently after different tests, the length of survival after undergoing different imaging tests, and the quality of patients' lives after different tests. No studies have provided comparative management or health outcome information in the context of diagnosis and staging of pancreatic adenocarcinoma.

The third important gap concerns the lack of evidence on important factors that could influence comparative accuracy, such as the prior experience of test readers (e.g., two tests may have similar accuracy if readers are very experienced, but one may be much better if readers are less experienced), patient factors (e.g., for patients with jaundice, one test may be better, but for patients without jaundice that same test is worse), and tumor characteristics (e.g., for staging small tumors, one test is best, but for large tumors, another test is best). Again, no studies provided pertinent data, so the reason for this gap also is insufficient or imprecise information.

The fourth important gap concerns the screening of asymptomatic high-risk people. No studies have reported test-specific screening accuracy (insufficient or imprecise information). This is an important gap in the literature because there is little evidence to justify the choice of one screening test over another.

Conclusions

We have comprehensively reviewed the evidence on commonly used imaging tests for the diagnosis and staging of pancreatic adenocarcinoma, as well as screening for pancreatic adenocarcinoma in high risk individuals. Some conclusions are possible at this time, specifically regarding relative test accuracy for different clinical purposes, but many uncertainties remain. Chief among these are the impact of imaging tests on patient management and long-term survival, the influence of patient factors and tumor characteristics on comparative accuracy, and test accuracy when used for screening high risk individuals.

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Introduction

Background

Pancreatic Adenocarcinoma

Pancreatic cancer is the fourth most common cause of cancer death among men and women in the United States.^{1,2} In 2013 in the United States, about 46,000 people received a diagnosis of pancreatic cancer and 40,000 died of the disease.³ The median age at diagnosis is 71 years, the overall 5-year survival is 5.8 percent, and the overall age-adjusted mortality rate is 10.8 per 100,000 people per year.^{4,5} The most common type of pancreatic cancer is adenocarcinoma (approximately 90% of all pancreatic malignancies).² Based on rates from 2007 to 2009, the lifetime risk of receiving a diagnosis of pancreatic cancer is 1.47 percent.⁵

Risk factors for pancreatic cancer include tobacco use; personal history of chronic pancreatitis, diabetes, obesity; and a family history of pancreatic cancer.¹ About 10 percent of patients with pancreatic cancer have a positive family history for the disease.⁴ Pancreatic cancer is also a disease of aging and median age at diagnosis is 71.

Pancreatic cancer incidence rates were reportedly highest among African-American men (21.3 per 100,000) and women (17.6 per 100,000) during 2004 and 2008.¹ The second highest rates were reported for Caucasian men (16.8 per 100,000) and women (12.8 per 100,000).¹ The differences between these populations and burden of disease may be related to higher rates of cigarette smoking and diabetes mellitus among African American men than for Caucasian men and higher body mass indices among African American women than for Caucasian women.¹

Diagnosis and Staging

Patients often remain asymptomatic or have only nonspecific symptoms such as malaise, fatigue, and loss of appetite until relatively late in the course of the disease, often with extensive spread, when weight loss, jaundice, and severe abdominal pain often appear. Due to late diagnosis, approximately 80 percent to 85 percent of cases are unresectable (i.e., too advanced to permit surgical resection),⁶ and the median survival of patients with unresectable tumors is only 6–10 months.⁷

Common symptoms leading to suspicion of pancreatic cancer are jaundice, epigastric pain, and weight loss;⁸ however, these symptoms are not specific. For example, in one study of 70 patients suspected of having pancreatic cancer, only 30 actually had pancreatic cancer; of the other 40, 16 had irritable bowel syndrome, 9 had other intra-abdominal cancers, 8 had pancreatitis, and 7 had other conditions.⁹ Thus, additional clinical information, including imaging tests, laboratory values, and biopsies, are important to differentiate these conditions from pancreatic cancer.

For the patient, given the poor prognosis of most cases, the differences in modalities and the consequences of their use are important to understand. Currently, there are no widely-accepted clinical practice guidelines that address which imaging modalities to use in the diagnosis and staging of pancreatic cancer. Also, elucidating patients' experience and tolerance of various imaging modalities may help future patients weigh the benefits and harms of the tests and allow them to incorporate their values and priorities. Once pancreatic adenocarcinoma is diagnosed, the stage of disease is a key determinant of clinical management, as well as a key predictor of survival. Most cases are diagnosed at an advanced stage, precluding surgical resection.¹ For

localized disease, the 5-year survival is approximately 22 percent.¹ When pancreatic adenocarcinoma is diagnosed at an advanced stage, the 5-year survival is approximately 2 percent.¹

The most commonly used system for staging pancreatic adenocarcinoma is the 2010 American Joint Committee on Cancer (AJCC) system:¹⁰

- Stage 0: carcinoma in situ, with neither lymph node involvement nor metastasis
- Stage IA: a ≤ 2 cm tumor limited to the pancreas, with neither lymph node involvement nor metastasis
- Stage IB: a > 2 cm tumor limited to the pancreas, with neither lymph node involvement nor metastasis
- Stage IIA: any size tumor that extends beyond the pancreas but does not involve either the celiac axis or the superior mesenteric artery (SMA), and with neither lymph node involvement nor metastasis
- Stage IIB: the same as IIA, except the lymph nodes are involved
- Stage III: any size tumor that involves the celiac axis or SMA, any lymph node status, and no metastases
- Stage IV: any size tumor and any lymph node involvement, and metastasis

An exact staging process before surgery (i.e., assigning the patient to stage I/II/III/IV) for pancreatic adenocarcinoma might not be performed, and the disease is often deemed resectable or unresectable intraoperatively. For unresectable cases, however, a biopsy is taken and a formal stage is determined to guide the planning of treatment modalities such as chemotherapy and potentially radiation.

Resectability

Surgical resection offers the only hope of cure and is decided via multidisciplinary consultation (e.g., surgeon, gastroenterologist, radiologist, oncologist, radiation oncologist). The two key factors in assessment of resectability are distant metastasis (which usually indicates unresectability) and blood vessel involvement (which sometimes indicates unresectability, depending on the degree of involvement). The major blood vessels of focus are the superior mesenteric vein (SMV), portal vein, celiac artery, common hepatic artery, and SMA. According to the 2012 guideline from the National Comprehensive Cancer Network (NCCN) on pancreatic adenocarcinoma:¹¹

- A resectable tumor shows no involvement of either the SMV or portal vein and shows “clear fat planes” around the celiac axis, hepatic artery, and SMA, and there are no distant metastases.
- An unresectable tumor has > 180 degrees SMA encasement or any celiac abutment, or an unreconstructible SMV/portal vein occlusion, or any aortic invasion/encasement, or any distant metastases.
- A “borderline” resectable tumor fits neither of the above two categories (e.g., some abutment of SMV/portal vein, < 180 SMA abutment). For these cases, NCCN recommends biopsy and possible neoadjuvant chemotherapy, which may shrink the tumor and permit subsequent resection.

These criteria continue to evolve, as surgical techniques advance and more tumors are resectable via reconstruction of blood vessels.¹²

Regarding the interface between stage and resectability, AJCC and others state that stages I and II are resectable, but stages III and IV are not.^{10,13} However, others believe that minor arterial involvement (stage III) may still permit resection.^{12,14} Vincent et al. (2011)¹⁴ argued that some stage III cases are borderline resectable and may be appropriate targets for neoadjuvant therapy followed by consideration of resection.

In judging resectability, multidisciplinary teams may perform optimally if the radiology reports present all of the key information in a standardized format. Such a format, specific to staging for pancreatic adenocarcinoma, was proposed in a 2014 consensus statement from the Society of Abdominal Radiology and the American Pancreatic Association.¹⁵ This statement provides a comprehensive list of the critical imaging findings, using common terminology that should be summarized by radiologists.

Screening

Screening for pancreatic adenocarcinoma is not recommended for the general population (e.g., the U.S. Preventive Services Task Force gives a D recommendation).¹⁶ However, some recommend screening those who are at high risk of developing pancreatic cancer. One report¹⁷ suggested that having two or more first-degree relatives with pancreatic cancer is sufficient justification for considering a screening test (or 3 or more blood relatives, one of whom is a first-degree relative). Further, some genetic risk factors (e.g., Peutz-Jeghers syndrome; *BRCA2*, *PALB2*, *p16* gene mutations; Lynch syndrome) motivate testing when the patient also has had a first-degree relative with pancreatic cancer.¹⁷

Imaging Technologies

The following sections describe imaging tests to assist diagnosis and/or staging of pancreatic adenocarcinoma, including multidetector computed tomography (MDCT), endoscopic ultrasound with fine-needle aspiration (EUS-FNA), positron emission tomography–computed tomography (PET/CT), and magnetic resonance imaging (MRI). The various available imaging modalities in the diagnosis and staging of pancreatic adenocarcinoma have different strengths and potential benefits, weaknesses, and potential harms. At present, there does not appear to be universal standard as to which imaging modalities should be used in which cases. This could be, in part, because of the difficulty of diagnosing and managing such an aggressive cancer, as well as limitations in the relevant evidence. It may also be related to clinical utility, local availability, procedural costs, and acceptability to patients.

Multidetector Computed Tomography

An MDCT scan is often the first imaging test in a patient whose symptoms suggest pancreatic adenocarcinoma. It provides three-dimensional multiplanar reconstruction images enabling determination of tumor size, extent, and spread, with a standardized pancreas protocol.^{18,19} The test does not always differentiate malignant from benign pancreatic lesions, and its ability to detect small tumors or small hepatic/peritoneal metastases is limited. A concern about MDCT is that the procedure exposes the patient to radiation and, therefore, may increase future cancer risk. Also, the quality of the computed tomography (CT) protocol, as well as the experience and expertise of the radiologist reading the CT may influence the accuracy of MDCT for diagnosis and staging of pancreatic adenocarcinoma. The American College of Radiology offers a voluntary accreditation program for CT facilities.²⁰

One notable type of MDCT is MDCT with angiography with or without three-dimensional (3D) reconstruction.²¹ This technology permits more precise imaging of blood vessels than standard MDCT. This report refers to MDCT without angiography as simply “MDCT.”

Endoscopic Ultrasound with Fine-Needle Aspiration

For EUS-FNA, an ultrasound transducer, which is positioned at the endoscope tip, is directly applied against the duodenal or gastric wall. This minimizes intervening adipose tissue and air that must be traversed by the ultrasound, therefore enhancing the image quality. This allows EUS to access and image the entire pancreas, the related vasculature, lymph nodes, and portions of the liver. The endoscopist can take a small aspiration (FNA) of any suspicious lesions, permitting cytologic evaluation. If the biopsy is adequate, EUS-FNA can distinguish benign from malignant lesions and characterize certain types of lesions (e.g., cystic pancreatic lesions).¹¹ Reported disadvantages of EUS-FNA include the procedure’s invasiveness, dependence on the skill of the endoscopist, and inability to evaluate for distant metastases.¹⁹ The relative newness of EUS-FNA could mean large variation in endoscopists’ technical skills. Potential patient harms related to EUS-FNA include perforation and bleeding, pancreatitis, and adverse effects related to sedation. The American College of Radiology has instituted a voluntary general ultrasound accreditation program that offers facilities the opportunity for peer review of their staff qualifications, equipment, and quality control and quality assurance programs.²²

We note that some centers may still perform EUS without the ability to take an FNA. Consultations with our Technical Expert Panel indicated that most EUS centers in the United States are equipped with FNA technology. Therefore, we focused on studies that had the potential to perform FNA. In the literature, there is current debate about whether an endoscopist should actually take an FNA of a resectable lesion.²³ For our report, we defined EUS-FNA as the procedural ability to take FNA, not the requirement that all lesions must have been sampled by FNA.

Magnetic Resonance Imaging

MRI is an alternative to MDCT as an initial imaging test for patients with a clinical suspicion of pancreatic adenocarcinoma or to evaluate the extent of disease. During an MRI procedure, electromagnetic fields and radiofrequency radiation translate hydrogen nuclei distribution in body tissues into images of anatomic structure. Similar to MDCT, a standardized pancreas protocol is available. MRI may be helpful when characterizing small (less than 1 cm) hepatic lesions, differentiating an inflammatory pancreatic mass from pancreatic adenocarcinoma, or detecting metastases to the liver.¹⁹ MRI can also be used as an adjunct to CT to better detect extrahepatic disease.^{24,25} There is no nationwide compulsory accreditation for MRI facilities. The American College of Radiology administers a voluntary accreditation program.²⁶

Positron Emission Tomography–Computed Tomography

PET is a whole-body scan whose image highlights places where a radioisotope tracer concentrates and is, therefore, particularly useful for detecting distant metastases. The most commonly used radioisotope tracer is fluorodeoxyglucose ¹⁸F (FDG). FDG-PET can locate metabolically active sites such as malignant tumors or sites with inflammation and may, therefore, help distinguish malignant tumors from benign pancreatic cysts or other masses not metabolically active. FDG-PET and CT can be combined to add precise anatomic localization (from CT) to functional data (from PET). The two scans are acquired concurrently, and the data

from each are merged. The Intersocietal Accreditation Commission (formerly the Intersocietal Commission for the Accreditation of Nuclear Medicine Laboratories [ICANL]) offers voluntary accreditation to PET/CT facilities based on a peer review of their staff qualifications, education, equipment, quality control, and number of clinical procedures.²⁷

Objectives of This Review

This review concerns imaging tests to identify and diagnose suspected pancreatic cancer in symptomatic or asymptomatic high-risk patients, and determine stage and surgical resectability of the disease.^{4,28} Pancreatic adenocarcinoma is fatal if untreated, so it is critical to choose the right imaging test and initiate therapy in a timely manner. Understanding the accuracy and characteristics of the various imaging tests may help elucidate in which specific circumstances certain imaging test may be more appropriate than others in given clinical situations. A comparative effectiveness review (CER) on this topic can assist medical decisions in several ways:

- First, different imaging tests are used for overlapping purposes. Thus, a critical issue is that when two tests are used for the same purpose (e.g., assessment of vessel involvement) in the same patients, which is more accurate? Answering this question may reduce practice variability and improve patient care.
- Second, the evidence may favor some tests over others, and if so, resources can be devoted to the better tests.
- Third, it is important to clarify the practice of using a second imaging test: under what circumstances to order a second test, and if so, which test to order; and if ordered, what is its influence on diagnosis, staging, survival, and quality of life.
- Fourth, the comparative accuracy of imaging tests depends on the operator's and reader's skills and the environment in which the test is performed (e.g., high-volume vs. low-volume centers). Determining the extent to which this is important for various tests can also help better guide clinicians and patients in the workup process.
- Fifth, harms are always a concern, and by estimating the actual rates of various harms of different imaging tests, a CER can help discriminate reasonable fears from unreasonable ones.

Scope and Key Questions

Key Questions

1. What is the comparative effectiveness of imaging techniques (e.g., MDCT, MDCT angiography, EUS-FNA, PET/CT, MRI) for *diagnosis* of pancreatic adenocarcinoma in adults with suspicious symptoms?
 - a. What is the accuracy of each imaging technique for diagnosis and assessment of resectability?
 - b. What is the comparative accuracy of the different imaging techniques for diagnosis and assessment of resectability?
 - c. What is the comparative diagnostic accuracy of using a single imaging technique versus using multiple imaging techniques?

- d. How is test experience (e.g., operative experience, assessor experience, center's annual case volume) related to comparative diagnostic accuracy of the different imaging strategies?
 - e. How are patient factors and tumor characteristics related to the comparative diagnostic accuracy of the different imaging strategies?
 - f. What is the comparative clinical management after the different imaging strategies when used for diagnosis?
 - g. What is the comparative impact of the different imaging strategies on long-term survival and quality of life when used for diagnosis?
2. What is the comparative effectiveness of imaging techniques (e.g., MDCT, MDCT angiography, EUS-FNA, PET/CT, MRI) for **staging** of pancreatic adenocarcinoma among adults with a diagnosis of pancreatic adenocarcinoma?
 - a. What is the staging accuracy of each imaging technique (for tumor size, lymph node status, vessel involvement, metastases, stage I–IV, and resectability)?
 - b. What is the comparative staging accuracy among the different imaging techniques?
 - c. What is the comparative staging accuracy of using a single imaging technique versus using multiple imaging techniques?
 - d. How is test experience (e.g., operative experience, assessor experience, center's annual volume) related to comparative staging accuracy of the different imaging strategies?
 - e. How are patient factors and tumor characteristics related to the comparative staging accuracy of the different imaging strategies?
 - f. What is the comparative clinical management of the different imaging strategies when used for staging?
 - g. What is the comparative impact of the different imaging strategies on long-term survival and quality of life when used for staging?
 3. What are the rates of harms of imaging techniques (e.g., MDCT, MDCT angiography, EUS-FNA, PET/CT, MRI) when used to diagnose and/or stage pancreatic adenocarcinoma?
 - a. How are patient factors related to the harms of different imaging techniques?
 - b. What are patient perspectives on the tolerance of different imaging techniques and the balance of benefits and harms of different imaging techniques?
 4. What is the screening accuracy of imaging techniques (e.g., MDCT, MDCT angiography, EUS-FNA, PET/CT, MRI) for detecting precursor lesion(s) of pancreatic cancer or pancreatic adenocarcinoma in high-risk asymptomatic adults (i.e., those at genetic or familial risk of pancreatic adenocarcinoma)?

Patients, Interventions, Comparisons, and Outcomes

Table 1 below summarizes the PICO (population, interventions, comparators, outcomes) for each key question. In the table, population P1 is symptomatic patients being assessed for possible pancreatic adenocarcinoma; population P2 is adults with known pancreatic adenocarcinoma; population P3 is asymptomatic adults at high risk of developing pancreatic adenocarcinoma. Regarding timing, the only issue concerns the outcomes of long-term survival and quality of life; we defined “long-term” as 1 year or more.

Table 1. PICO for each Key Question

KQ	Population	Interventions	Comparators	Outcomes
1a	P1	MDCT, MDCT angiography, EUS-FNA, PET/CT, or MRI	None	Diagnostic accuracy as determined by surgical findings and/or clinical followup Accuracy of resectability judgment
1b	P1	Same list of interventions as for KQ1a	Another test from the list of interventions as for KQ1a	Diagnostic accuracy as determined by surgical findings and/or clinical followup Accuracy of resectability judgment
1c	P1	Single imaging test: Same list of interventions as for KQ1a	Multiple tests from the list of interventions as for KQ1a	Diagnostic accuracy as determined by surgical findings and/or clinical followup
1d	P1	1 test: High vs. low experience	Another test: High vs. Low experience	Diagnostic accuracy as determined by surgical findings and/or clinical followup
1e	P1	Patient factors or tumor characteristics	Comparator patient factor (e.g., age) or tumor characteristic (e.g., head or tail of pancreas)	Diagnostic accuracy as determined by surgical findings and/or clinical followup
1f	P1	Same list of interventions as for KQ1a	Same list of interventions as for KQ1a	Clinical management (e.g., the percentage of patients in whom resection is attempted)
1g	P1	Same list of interventions as for KQ1a	Same list of interventions as for KQ1a	Overall survival (minimum 1 year followup) Pancreatic adenocarcinoma-specific survival (minimum 1 year followup) Quality of life (e.g., SF-36) (minimum 1 year followup)
2a	P2	Same list of interventions as for KQ1a	None	Staging accuracy as determined by surgical findings and/or clinical followup: <ul style="list-style-type: none"> • T stage • N stage • M stage • Stage I–IV • Vessel involvement • Resectability

Table 1. PICO for each Key Question (continued)

KQ	Population	Interventions	Comparators	Outcomes
2b	P2	Same list of interventions as for KQ1a	Another test from the list of interventions as for KQ1a	Staging accuracy as determined by surgical findings and/or clinical followup (same list as above)
2c	P2	Single imaging test: Same list of interventions as for KQ1a	Multiple imaging tests: Same list of interventions as for KQ1a	Staging accuracy as determined by surgical findings and/or clinical followup (same list as above)
2d	P2	1 test: High vs. low experience	Another test: High vs. Low experience	Staging accuracy as determined by surgical findings and/or clinical followup (same list as above)
2e	P2	1 test: Effect of patient factor or tumor characteristic	Another test: Effect of patient factor or tumor characteristic	Staging accuracy as determined by surgical findings and/or clinical followup (same list as above)
2f	P2	Same list of interventions as for KQ1a	Same list of interventions as for KQ1a	Clinical management (e.g., the percentage of patients in whom resection is attempted)
2g	P2	Same list of interventions as for KQ1a	Same list of interventions as for KQ1a	Overall survival (minimum 1 year followup) Pancreatic adenocarcinoma-specific survival (minimum 1 year followup) Quality of life (e.g., SF-36) (minimum 1 year followup)
3	P1 or P2 or P3	Same list of interventions as for KQ1a	None	Radiation from MDCT (e.g., carcinogenic effects) Adverse reactions to contrast agents Adverse reaction to radiopharmaceuticals Pancreatitis from EUS-FNA Perforation or bleeding from EUS-FNA. Sedation-related effects of EUS-FNA (e.g., nausea, vomiting)
3a	P1 or P2 or P3	Patient factor	Comparator patient factor	See above list of harms
3b	P1 or P2 or P3	Same list of interventions as for KQ1a	Any	Patient perspectives on imaging techniques, including tolerance, satisfaction, preference, and balance of benefits and harms
4	P3	Same list of interventions as for KQ1a	Same list of interventions as for KQ1a	Screening accuracy as determined by surgical findings and/or clinical followup

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration; KQ = Key Question; M = metastasis stage; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; N = nodal stage; PET/CT = position emission tomography-computed tomography; T = tumor stage.

Note: Population P1 is symptomatic patients being assessed for possible pancreatic adenocarcinoma; population P2 is adults with known pancreatic adenocarcinoma; population P3 is asymptomatic adults at high risk of developing pancreatic adenocarcinoma. High risk encompasses those with either a genetic or familial risk such as having two or more first-degree relatives with pancreatic cancer; three or more blood relatives, one of whom is a first-degree relative; or in addition to having a first-degree relative with pancreatic cancer, having Peutz-Jeghers syndrome, Lynch syndrome, or *BRCA2*, *PALB2*, or *p16* gene mutations.

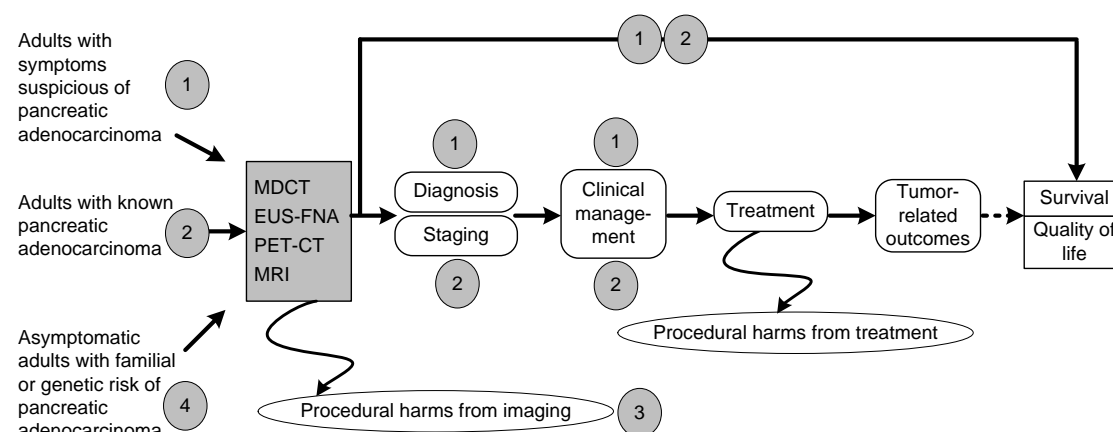
Conceptual Framework

An analytic framework illustrating the connections between the populations of interest, the imaging techniques, and the outcomes is shown in Figure 1 below. Populations that are undergoing or have undergone treatment for pancreatic adenocarcinoma are outside the scope of this report.

The populations of interest enter the diagram at the left, undergo diagnosis (Key Question 1), staging (Key Question 2), and then commence treatment. Some outcomes such as test performance can be measured immediately after performing the tests, but the most important outcomes (such as long-term survival and quality of life) are measured after completion of treatment.

An important factor in selecting an imaging modality is the availability and accessibility of that modality. Although this factor will not be addressed formally in the review via a key question, we plan to collect and provide relevant information about the availability and accessibility of imaging modalities and information about current patterns of care, as available. This information will be presented in the background and discussion sections to help place the evidence review findings in context.

Figure 1. Analytic framework



Note: Circled numbers, e.g., 1 denote Key Questions addressed by the systematic review. MDCT – Multidimensional computed tomography; EUS-FNA – Endoscopic ultrasound with fine needle aspiration; PET-CT – Simultaneous positron emission tomography and computed tomography; MRI – Magnetic resonance imaging

This figure depicts the Key Questions within the context of the PICOTS below. In general, the figure illustrates how different types of patients (the three populations listed on the left) can undergo different imaging tests (large box), resulting in the intermediate outcomes of diagnostic accuracy, staging accuracy, and clinical management decisions. Treatment is intended to improve (if possible) the patient-oriented outcomes listed to the right: survival and quality of life. Also, procedural harms of the imaging procedures may occur.

Organization of This Report

In the remaining three chapters of this report, we present the methods for this systematic review, the results for each key question, and a discussion of the findings. Within the Results chapter, we provide the results of the literature searches and selection procedures, then the results for Key Question (KQ) 1.

For the comparative accuracy of imaging tests (KQ1b and KQ2b), each section is divided per comparison (e.g., first we present the evidence on MDCT vs. EUS-FNA, then the evidence on MDCT vs. MRI). Within each of those subsections, we consider different aspects of the clinical process (e.g., for staging, we first consider the evidence on T staging, then evidence on N staging).

The Discussion section, which appears after all Results sections, provides an overview of our findings, and how they relate to what is already known. In that section we also discuss implications for clinical and policy decisionmaking, the applicability of the evidence, limitations of our review as well as limitations of the evidence we reviewed, and any major gaps in existing research.

Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>). The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist.²⁹

Topic Refinement and Review Protocol

Initially a panel of key informants gave input on the Key Questions (KQs) to be examined; these KQs were posted on AHRQ’s website for public comment between February 26, 2013, and March 25, 2013, and revised as needed. We then drafted a protocol for the CER and recruited a panel of technical experts to provide high-level content and methodological expertise throughout the development of the review.

Literature Search Strategy

Medical librarians in the Evidence-based Practice Center (EPC) Information Center performed literature searches, following established systematic review protocols. We searched the following databases using controlled vocabulary and text words: Embase, MEDLINE, PubMed, and The Cochrane Library from 1980 through November 1, 2013. The full search strategy is shown in Appendix A.

Literature screening (for reviews or studies) was performed in duplicate using the database Distiller SR (Evidence Partners, Ottawa, Canada). Initially, we screened literature search results in duplicate for relevancy. We screened relevant abstracts again, in duplicate, against the inclusion criteria. Studies that appeared to meet the inclusion criteria were retrieved in full, and we screened them again, in duplicate, against the inclusion criteria. All disagreements were resolved by consensus discussion among the two original screeners and, if necessary, an additional third screener. For procedural harms of imaging technologies of interest, we conducted a supplemental search that was not limited to the literature on pancreatic adenocarcinoma. We used Reference Manager[™] software (Thomson Reuters, New York, NY) for managing references.

The literature searches will be updated during the peer review process, before finalization of this comparative effectiveness review (CER).

Study Selection

Our criteria are listed in five categories below: (1) publication criteria, (2) study design criteria, (3) patient criteria, (4) test criteria, and (5) data criteria.

Publication Criteria:

- a. Full-length articles: The article must have been published as a full-length peer-reviewed study. Abstracts and meeting presentations were not included because they do not include sufficient details about experimental methods to permit an evaluation of study design and conduct, and they may also contain only a subset of measured outcomes.^{30,31} Additionally, it is not uncommon for abstracts that are published as part of conference

proceedings to have inconsistencies when compared with the final publication of the study or to describe studies that are never published as full articles.³²⁻³⁶

- b. Redundancy: To avoid double-counting of patients, in instances in which several reports of the same or overlapping groups of patients were available, only outcome data based on the larger number of patients were included. However, we included data from publications with lower numbers of patients when either (a) a publication with lower patient enrollment reported an included outcome that was not reported by other publications of that study, or (b) a publication with lower patient enrollment reported longer followup data for an outcome.
- c. English language: Moher et al. (2000) have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn.³⁷ Juni et al. (2002) found that non-English studies typically were of higher risk of bias and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined.³⁸ Although we recognize that in some situations, exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translation of studies.
- d. Publication date: We included studies published since January 1, 2000. We thought that older articles would include outdated technologies. Studies of harms of imaging technologies that did not specifically involve pancreatic adenocarcinoma (i.e., any clinical indication), must have been published since January 1, 2009. We chose this more recent date because we anticipated a large number of studies of imaging in patients with any clinical condition.

Study Design Criteria:

- a. For KQs on single-test accuracy: For KQs 1a and 1b, which address the performance of a single imaging test against a reference standard, we included only systematic reviews. EPC guidance by White et al. (2009)³⁹ states how existing systematic reviews can be used to replace de novo processes in CERs. We will refer to the PICOTS-SD for the pertinent subquestion, and these seven components (Populations, Interventions, Comparisons, Outcomes, Time Points, Setting, Study design) will be the seven inclusion criteria. For quality, see the end of Appendix D on risk of bias.
- b. For any KQs comparing two or more tests, the study must have compared both tests to a reference standard. The reference standard must not have been defined by either imaging test being assessed.
- c. For any KQs on single versus multiple tests, test experience, patient factors (e.g., age), or tumor characteristics (e.g., head or tail of pancreas), the study must have made a comparison of data to address the question. For example, for test experience, the difference between multidetector computed tomography (MDCT) and endoscopic ultrasound with fine-needle aspiration (EUS-FNA) may depend on the experience of the centers (e.g., higher case-volume centers may find less of a difference in these technologies than lower case-volume centers).
- d. For any KQs involving comparative clinical management or long-term survival or quality of life, some patients must have received one of the imaging tests, and a separate group of patients must have received a different imaging test. This design permits a comparison of how the choice of test may influence management and/or survival and/or quality of life.
- e. For KQ3 on the rates of procedural harms, we included any reported harms data based on 50 or more patients, in the context of diagnosis or staging of pancreatic adenocarcinoma,

on the harms of imaging procedures that contained a statement in the Methods section that the study planned in advance to capture harms/complications data. Additionally, we included studies primarily of harms and adverse events associated with the use of each specific imaging modality, regardless of the type of cancer being detected, that were published in 2009 or later.

- f. For KQ3b on patient perspectives of imaging tests, any study design was accepted.
- g. For KQ4 on screening, we included any study that reported the performance of at least one included imaging test in the context of screening for either pancreatic adenocarcinoma itself or precursor lesions to pancreatic cancer.

Patient Criteria:

- a. To be included, the study must have reported data obtained from groups of patients in which at least 85 percent of the patients were from one of the patient populations of interest. If a study reported multiple populations, it must have reported data separately for one or more of the populations of interest.
- b. Adults. At least 85 percent of patients must have been aged 18 years or older, or data must have been reported separately for those aged 18 years or older.
- c. Studies of screening, diagnosing, or staging *primary* pancreatic adenocarcinoma were included. Testing for *recurrent* pancreatic cancer was excluded.
- d. Data on imaging tests performed after any form of treatment (e.g., neoadjuvant chemotherapy) were excluded, but pretreatment imaging data were considered.

Test Criteria:

- a. Type of test. Only studies of the imaging tests of interest were included (listed in the KQs above). Studies of computed tomography (CT) that did not explicitly state that (or it could not be determined that) CT was MDCT were assumed to be MDCT. Given our publication date criterion of 2000 and later, we believe it safe to assume that CT performed in such studies was MDCT.

Data Criteria:

- a. The study must have reported data pertaining to one of the outcomes of interest (see the KQs section).
 - For accuracy outcomes (KQ1a through 1e; KQ2a through 2e, and KQ4), this means reporting enough information for one to calculate both sensitivity and specificity, along with corresponding confidence intervals.
 - For clinical management (KQ1f, KQ2f), this means reporting the percentage of patients who received a specific management strategy, after undergoing each imaging test (a separate group of patients corresponding to each imaging test).
 - For long-term survival (KQ1g, KQ2g), this means either reporting median survival after each imaging test (separate groups of patients), or mortality rates at a given time point (separate groups of patients), or other patient survival such as a hazard ratio.

- For quality of life (KQ1g, KQ2g), this means reporting data on a previously tested quality-of-life instrument (such as the SF-36) after each imaging test (separate groups of patients).
 - For harms (KQ3), this means a statement appearing in the Methods section that harms/complications would be measured, reporting the occurrence of a procedure-related harm and the number of patients at risk, or the reporting that no harms or complications occurred as a result of the procedure.
 - For patient perspectives (KQ3b), this means reporting the results of asking patients about their opinions or experience after having undergone one or more of the imaging tests.
- b. Regarding the minimum patient enrollment, for studies comparing imaging tests (KQ1b through 1g and KQ2b through 2g), we required data on at least 10 patients per imaging test. We also used a minimum of 10 for KQ3b on patient perspectives of imaging tests. We used a minimum of 50 patients for data on harms (KQ3) or screening (KQ4).
 - c. For all KQs, the reported data must have included at least 50 percent of the patients who had initially enrolled in the study.
 - d. Studies that reported data by tumor (e.g., x percent of pancreatic adenocarcinoma *tumors* were correctly detected) instead of by patient (e.g., x percent of enrolled *patients* were correctly given a diagnosis of pancreatic adenocarcinoma) were not excluded for this difference. However, the tumor-based data was separated from the patient-based data because they measure different types of accuracy.

Data Abstraction

We abstracted information from the included studies using Microsoft Excel (Redmond, WA) and we extracted the data into these forms. Duplicate abstraction of comparative accuracy data was used to ensure accuracy. All discrepancies were resolved by consensus discussion. Elements to be abstracted included general study characteristics (e.g., country, setting, study design, enrolled number), patient characteristics (e.g., age, sex, comorbidities), details of the imaging methodology (e.g., radiotracer, timing of test), risk-of-bias items, and outcome data. Appendix C contains all evidence tables except those involving risk of bias, which appear in Appendix D.

Risk of Bias Evaluation

For systematic reviews of single-test accuracy, EPC guidance by White et al. (2009)³⁹ suggests that EPCs assess the quality of an existing systematic review by using a revised AMSTAR (Assessment of Multiple Systematic Reviews) instrument. The items we used for this appear in Appendix D. For each included review, two analysts independently answered 15 items and independently assigned the review as either high quality or not high quality (thus for systematic reviews, we made no distinction between moderate and low quality). Discrepancies in the category assignment were resolved by consensus. A review was considered high quality if it met eight specific items (see Appendix D). When systematic reviews did not meet these eight items, we considered them not high quality.

For studies comparing two or more tests, we used a set of nine risk-of-bias items after considering the QUADAS-2, as well as additional issues that specifically address bias in the

comparison of diagnostic tests to differentiate between high, medium or low risk of bias (see Appendix D).

Strength of Evidence Grading

We used the EPC system for grading comparative evidence from primary studies on diagnostic tests as described in the EPC guidance chapter by Singh et al. (2012).⁴⁰ This system uses up to eight domains as inputs (risk of bias, directness, consistency, precision, publication bias, dose-response association, all plausible confounders would reduce the effect, strength of association). The output is a grade of the strength of evidence: high, moderate, low, or insufficient. This grade is made separately for each outcome of each comparison of each KQ. Definitions for these categories is provided in Table 2 below. Strength of evidence final grades (as well as each component that contributed to each grade) are provided in a table of the Conclusion section for the pertinent KQ.

Table 2. Strength of evidence grades and definitions

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, that is, another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Source: Singh et al. (2012).⁴⁰

The EPC system requires that reviewers select the most important outcomes of a review to be graded. For this report, we graded evidence on comparative accuracy for diagnosis and staging, clinical outcomes (clinical management, survival, quality of life), and screening accuracy. These were the most important outcomes, and the EPC guidance chapter by Singh et al. (2012)⁴⁰ can be applied. We did not grade the strength of evidence from published systematic reviews on the accuracy of individual imaging tests, or the procedural harms of a single imaging test, or screening accuracy.

For each comparison and each outcome, we determined whether the evidence permitted an evidence-based conclusion. For comparative test accuracy, this meant whether the evidence was sufficient to permit one of the following three types of conclusions: (1) test A is more accurate than test B, (2) test B is more accurate than test A, or (3) tests A and B are similarly accurate. The first two types of conclusions required a statistically significant difference for either sensitivity or specificity (or both), whereas the third type of conclusion required a non-statistically-significant difference for both sensitivity and specificity, as well as independent judgments from two reviewers that the data were precise enough to indicate similar accuracy. If none of these three conclusions were appropriate, we graded the evidence insufficient. If the evidence was sufficient to permit a conclusion, then the grade was high, moderate, or low. The grade provided by two independent raters, and discrepancies were resolved by consensus. Below, we discuss the eight domains and how they were considered:

Study limitations. Study limitations indicate the extent to which studies included for a given outcome were designed and conducted to protect against bias. If the evidence permitted a conclusion, then all else being equal, a set of studies at low risk of bias yielded a higher strength of evidence grade than a set of studies at medium or high risk of bias. The study limitations domain represents the overall risk of bias for a set of studies, and is judged low, medium or high.

Directness. For questions on test accuracy, data on accuracy directly addressed the question, so those data were considered direct. For question on other outcomes (e.g., long-term survival), data on the actual outcomes were necessary for inclusion and to be judged direct.

Consistency. For questions comparing the accuracy of two or more tests, and for other comparative questions, consistency was judged based on whether the studies' findings suggested the same direction of effect.

Precision. For questions comparing the accuracy of two or more tests, and for other comparative questions, the evidence was considered sufficiently precise if the data showed a statistically significant difference (between groups or between tests) or if the data demonstrated similar results.

Reporting bias. This was addressed by noting the presence of abstracts or ClinicalTrials.gov entries describing studies that did not subsequently appear as full published articles. If many such studies exist, this will tend to decrease the strength of the evidence. We also considered the funding source of studies, and we performed any appropriate quantitative analyses correlating study effect sizes to the end of patient-enrollment dates.

Dose-response association. This domain was relevant only with respect to the radiation dose for CT. One possibility is that higher doses result in higher accuracy of CT. If the evidence shows that CT is more accurate than another imaging technique and that the difference is even larger in studies that used higher CT doses, it would generally increase the strength of evidence.

All plausible confounders would reduce the effect. This domain means that a set of studies may be biased *against* finding a difference between two interventions, and yet the studies still found an important difference. Thus, if the studies had controlled for the confounders, the effect would have been even larger. This domain was considered when statistical differences were found.

Strength of association. This domain was judged by EPC team members based on whether the size of a difference (e.g., the extent of difference in accuracy between two tests) was so large that the potential study biases could not explain it. If true, this domain will generally increase the grade of strength of evidence. This domain was considered when statistical differences were found.

Applicability

The applicability of the evidence involved four key aspects: patients, tests/interventions, comparisons, and settings. In considering the applicability of the findings to patients, we consulted large studies to ascertain the typical characteristics of patients newly given a diagnosis of pancreatic adenocarcinoma (e.g., age, sex) and then assessed whether the included studies enrolled similar patients. Some aspects of interventions may also affect applicability, for example if a study uses an uncommonly used radiotracer. Settings of care were described, and if data permitted, subgroups of studies by setting were analyzed separately. We did not provide categorical ratings of applicability, but instead we discussed applicability concerns in the Discussion section of the report.

Data Analysis and Synthesis

For comparing the accuracy of imaging tests, we synthesized the evidence on sensitivity and specificity using meta-analysis wherever appropriate and possible. Decisions about whether meta-analysis was appropriate were based on the judged clinical homogeneity of the different study populations, imaging and treatment protocols, and outcomes. Statistical heterogeneity was measured using tau-squared. When meta-analysis was not possible (because of limitations of reported data) or was judged to be inappropriate, the data were synthesized using a descriptive approach.

For each pair of imaging tests compared directly by a group of studies (e.g., MDCT and EUS-FNA) for a given clinical purpose (e.g., diagnosis), we performed bivariate meta-analysis of each test's accuracy data using the "metandi" command in STATA.⁴¹ If this model could not be fit for a given test (i.e., if there were 3 or fewer studies in the analysis or the model did not converge), we used Meta-Disc (freeware developed by the Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain).⁴² Using the meta-analytic results, we used equation 39 in Trikalinos et al. (2013)⁴³ to compare the tests statistically (separately for sensitivity and specificity). For these tests, we set $p=0.05$ (two-tailed) as the threshold for statistical significance. If a comparison was not statistically significant, two reviewers independently judged whether the confidence interval around the difference was sufficiently narrow to permit a conclusion of similar accuracy. We did not set the specific degree of narrowness required to permit an equivalence conclusion, since we could find no consensus in the field as to the minimal important difference in accuracy. Instead, this was a judgment made by two independent reviewers, with disagreements were resolved by consensus. When studies reported accuracy data for multiple readers separately, we first selected the data from reader 1 only, and performed sensitivity analyses of selecting all other permutations of readers. The selection of reader 1 was arbitrary.

Some data were reported in terms of whether the precise T stage (or the overall TNM) was correctly assessed by an imaging test. For these studies, we computed an odds ratio of accurate staging based on paired binary data and we assumed a test-test correlation of 0.5.

Peer Review and Publication

The review protocol was posted from August 9, 2013, to September 6, 2013, at Research Protocol. Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The dispositions of the peer review comments are documented and will be published 3 months after the publication of the Evidence report.

Results

Introduction

In this chapter, we describe the results of the literature searches, and then present the results for each KQ.

A list of acronyms and abbreviations is available following the list of references for this report, along with a glossary of selected terms. The Appendixes include Appendix A, Search Strategy; Appendix B, Full-length Review of Excluded Studies; Appendix C, Evidence Tables; Appendix D, Analyses and Risk of Bias Assessments, and Appendix E, Sensitivity Analyses for Meta-analyses Involving Multiple Readers per Study. In Appendix C:

- The tables of systematic reviews appear first (two for KQ1a, and two for KQ2a; sorted in reverse chronology and then by last name of the first author)
- The tables of comparative accuracy studies appear next, involving KQ1b and KQ2b. The first two tables present general study characteristics and patient characteristics, and are sorted in reverse chronology and then by last name of the first author. The next five tables provide test details, and are also sorted in reverse chronology and then by last name of the first author. The final table provides all the comparative accuracy data, and is first sorted by the component being assessed (e.g., vessel involvement), then by test comparison (e.g., MDCT vs. EUS-FNA), and finally by reverse chronology.
- The tables of harms studies appear next, involving KQ3, and are sorted in reverse chronology and then by last name of the first author. The first four tables summarize the pancreas-specific studies, and the others summarize the non-pancreas-specific studies.
- The tables of screening studies appear last, involving KQ4, and are sorted in reverse chronology and then by last name of the first author. The tables summarize general study characteristics, patient information, test details, and data.

Our quantitative analyses of comparative accuracy are summarized in Appendix D, along with the risk-of-bias assessments.

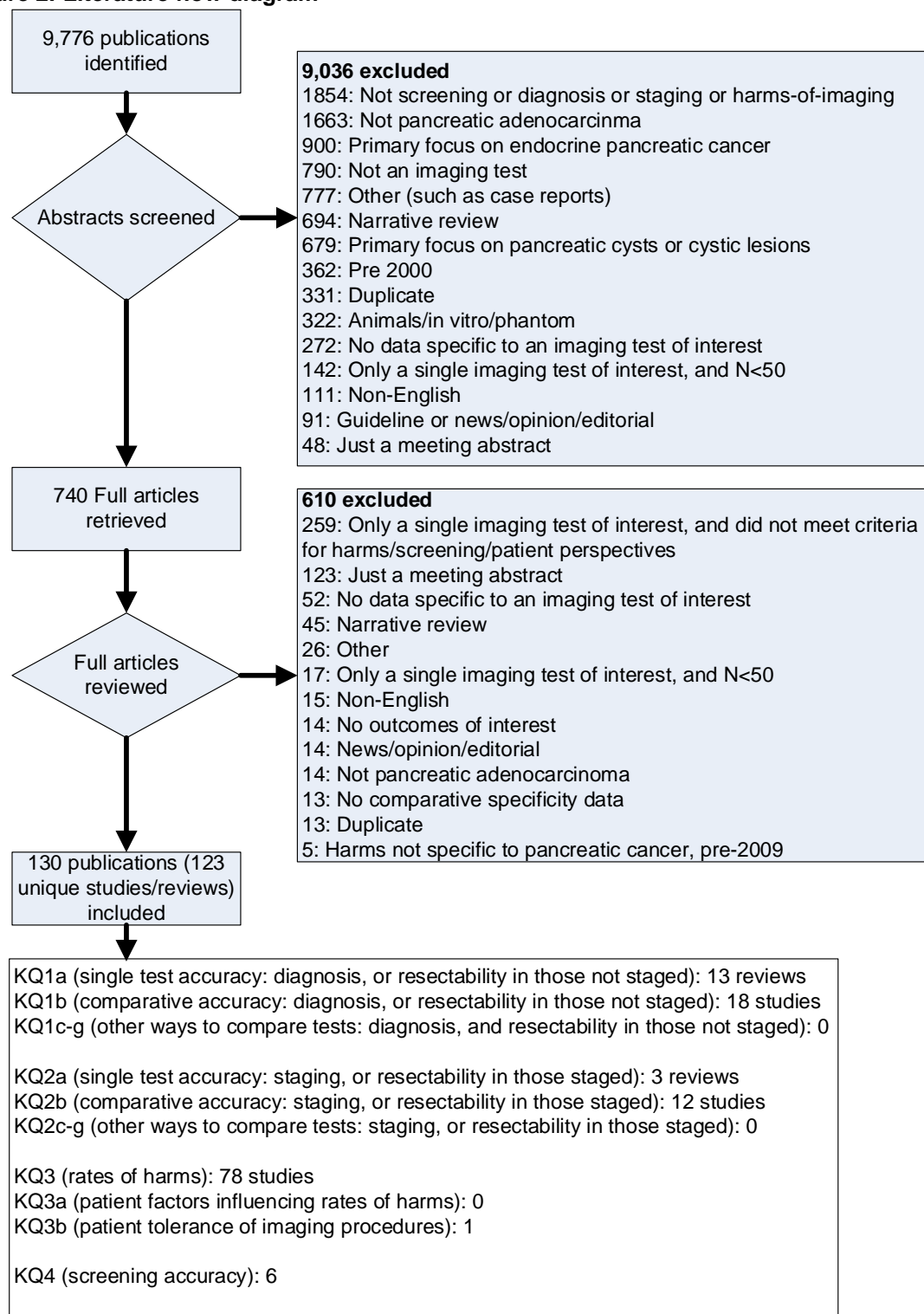
Results of Literature Searches

We summarize the study selection process in Figure 2 below (as recommended by Moher et al.[2009]).²⁹ The literature searches identified 9,776 citations, and after duplicate review, we excluded 9,036 of them. The most common reason for exclusion was that the article did not involve diagnosis, staging, screening, or harms. We retrieved the other 740 articles in full, and after duplicate review, we excluded 610 of those. The most common reason was that the study reported data on only a single imaging test of interest and did not meet inclusion criteria for other KQs. See Appendix B for a list of the publications excluded at the full article level. We included the remaining 130 publications, which described 123 unique studies/reviews (7 publications reported overlapping patients). Of the 123, 15 were systematic reviews and 108 were studies.

We sent scientific information packet (SIP) letters and emails to the 11 identified relevant industry stakeholders requesting submission of published and unpublished information on their product(s). Additionally, a U.S. Federal Register notice was posted on August 27, 2013, requesting scientific information submissions (<https://federalregister.gov/a/2013-20849>). Two

responses were subsequently received, and both responses indicated that the sender did not know of any pertinent studies.

Figure 2. Literature flow diagram



Note: the numbers in the box above add to more than 123 because some studies/reviews addressed multiple Key Questions.

Test Performance of Imaging Modalities for Diagnosis

KQ1: Comparative Effectiveness of Imaging Techniques for Diagnosis

KQ1a. What is the accuracy of each imaging technique for diagnosis and assessment of resectability?

Key Points

- Evidence was insufficient to permit accuracy estimates for multidetector computed tomography (MDCT) angiography with or without three-dimensional (3D) reconstruction.
- For diagnosis using MDCT, one systematic review yielded a sensitivity estimate of 91 percent (95% confidence interval [CI], 86% to 94%) and a specificity estimate of 85 percent (95% CI, 76% to 91%). (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using endoscopic ultrasound with fine-needle aspiration (EUS-FNA), four high-quality and recent systematic reviews yielded sensitivity estimates ranging from 85 percent to 93 percent and specificity estimates ranging from 94 percent to 100 percent. (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using magnetic resonance imaging (MRI), three systematic reviews yielded sensitivity estimates of 84 percent to 86 percent and specificity estimates of 82 percent to 91 percent. (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using positron emission tomography–computed tomography (PET/CT), three systematic reviews yielded sensitivity estimates of 87 percent to 90 percent and specificity estimates of 80 percent to 85 percent. (Strength of evidence from published systematic reviews was not graded.)
- For MDCT, in assessing the resectability of tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 81 percent (95% CI, 76% to 85%) and a specificity estimate of 82 percent (95% CI, 77% to 97%). (Strength of evidence from published systematic reviews was not graded.)
- For MRI, in assessing the resectability tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 82 percent (95% CI, 69% to 91%) and a specificity estimate of 78 percent (95% CI, 63% to 87%). (Strength of evidence from published systematic reviews was not graded.)

Detailed Synthesis

Thirteen systematic reviews⁴⁴⁻⁵⁶ met the inclusion criteria for this question, of which four were both recent (published 2009 or later) and of high quality (meeting all eight of the quality criteria deemed most important). All of the reviews are summarized in Appendix C, and their quality assessments are in Appendix D. The four recent high-quality reviews included only evidence on EUS-FNA and not on any of the other diagnostic modalities. The total number of included studies and patients for the four imaging technologies were:

- EUS-FNA: 58 studies, ~7,862 patients (precise counts not calculable because some reviews reported the study Ns differently)

- CT: At least 29 papers, at least 1,823 patients (precise counts not calculable due to unknown overlap between diagnostic and resectability studies)
- MRI: 25 papers, at least 1,169 patients (precise counts not calculable because one review did not provide sufficient information)
- PET-CT: 14 studies, 622 patients

Diagnosis

For EUS-FNA in diagnosing pancreatic cancer, we included eight reviews,^{44-47,52,54,55,57} and of these, the four recent high-quality reviews^{44,46,47,57} reported summary sensitivity results ranging from 85 percent to 93 percent and summary specificity results ranging from 94 percent to 100 percent (see Appendix C). A threshold effect was apparent, as the reviews reporting the highest specificities were also the ones reporting the lowest sensitivities. A threshold effect was also seen within Madhoun's review (2013),⁴⁴ as FNA with a 25-gauge needle resulted in higher sensitivity and lower specificity than FNA with a 22-gauge needle. The difference in sensitivity was statistically significant; the difference in specificity was not.

CT was addressed in only one review,⁵³ which was deemed not of high quality. It also is outdated, having been published in 2005.

MRI was addressed in three reviews,^{48,49,53} none of which were high quality. Two of the reviews^{48,49} were published by the same group of authors in different journals the same year. Study inclusion criteria in the two reviews were identical except for means of obtaining the reference diagnosis (histopathologic analysis only in 1 review,⁴⁸ histopathologic analysis or clinical and imaging followup in the other⁴⁹). All of the MRI studies included in the former review were also included in the latter. The reviews agreed on MRI sensitivity, with meta-analysis results ranging from 84 percent to 86 percent, but differed on specificity, with the two reviews from one group reporting 91 percent specificity and the other review reporting 82 percent. The difference may be because the most recent data in the third review⁵³ is now 10 years old, and thus it does not reflect the current state of the art in MRI.

PET/CT was addressed in three reviews,^{48,50,56} none of which were high quality. The review by Wu et al. (2012)⁴⁸ reported an erroneous confidence interval on sensitivity (82% to 81%), which is likely a typographical error. We attempted to contact the authors to obtain the correct confidence interval, but received no response.

Results across all modalities are summarized in Table 3. The limited quality of all the reviews on CT, MRI, and PET/CT preclude great confidence in the quantitative estimates of accuracy.

Table 3. KQ1a: Summary results of systematic reviews on diagnosis

Modality	MDCT	EUS-FNA	MRI	PET/CT
Number of reviews	1	8, and 4 were high quality	3 (2 mostly duplicative of each other)	3
Quality of reviews (based on revised AMSTAR)	Low	4 Low, 4 High	Low	Low
Most recent review	2005	2013	2012	2013
Range of results	Sensitivity: 91% Specificity: 85%	High quality reviews: Sensitivity: 85% to 93% Specificity: 94% to 100%	Sensitivity: 84% to 86% Specificity: 82% to 91%	Sensitivity: 87% to 90% Specificity: 80% to 85%

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; PET/CT = position emission tomography-computed tomography.

Resectability

The only review that included resectability as an outcome was outdated, not of high quality, and analyzed only MDCT and MRI studies (Table 4).⁵³

Table 4. KQ1a: Summary results of systematic reviews on resectability

Modality	MDCT	EUS-FNA	MRI	PET/CT
Number of reviews	1	0	1	0
Quality of reviews (based on revised AMSTAR)	Low	—	Low	—
Most recent review	2005	—	2005	—
Range of results	Sensitivity: 81% Specificity: 82%	—	Sensitivity: 82% Specificity: 78%	—

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; PET/CT = position emission tomography-computed tomography.

Comparative Test Performance of Imaging Modalities for Diagnosis

KQ1b. What is the comparative accuracy of the different imaging techniques for diagnosis and assessment of resectability?

Key Points

- MDCT and EUS-FNA have similar accuracy in the assessment of resectability of pancreatic adenocarcinoma in unstaged symptomatic adults (Strength of evidence: low)
- MDCT and MRI have similar accuracy in the diagnosis of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate)
- PET/CT is more accurate than MDCT in the diagnosis of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: low)

- For all other test comparisons involving diagnosis and the assessment of resectability in patients with unstaged disease, we deemed the evidence insufficient to permit conclusions, and the most common reason for insufficiency was imprecision.

Detailed Synthesis

Twenty-four studies met inclusion criteria for KQ1b or KQ2b on comparative accuracy for staging (or met criteria for both KQ1b and KQ2b). General study characteristics, patient characteristics, and test details appear in Appendix C. Ten of the 24 were conducted in Europe, 6 in the United States, 4 in Japan, and 4 in other countries. Nineteen of the 24 studies were conducted at universities. For the 19 studies reporting the dates of patient enrollment, the starting dates ranged from October 1995 to September 2008, and the median length of the patient enrollment period was 2 years (range 7 months to 5 years). Fifteen studies were prospective, and the other nine were retrospective. Eleven studies reported either the study funding source or whether there existed conflicts of interest (or both). Among these 11 studies, 6 specifically declared that authors had no conflicts of interest; 3 provided the funding source(s) but did not mention conflicts of interest; 2 reported that the authors had potential conflicts of interest. For these latter two—

- One study⁵⁸ comparing EUS-FNA to MDCT was authored by individuals receiving grant money from the American Society for Gastrointestinal Endoscopy, however, the authors stated that “the funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.”
- The other study,²¹ comparing MDCT angiography with or without 3D reconstruction stated: “There has been no industry or pharmaceutical support.” One of the authors had developed and patented the 3D reconstruction software being assessed.

Regarding study design, the 24 studies performed multiple imaging tests on a single group of patients. One key advantage of this design is that patient factors and tumor characteristics are controlled; any observed difference in the accuracy of the tests could not be attributed to differences in the types of patients who received those tests (e.g., differences in tumor size profiles). The remainder of this section is divided into subsections based on the comparisons made by included studies (listed in Table 5 below).

Table 5. KQ1b: numbers of studies comparing different tests for diagnosis and resectability in patients with unstaged disease

Comparison	Number of Studies of Diagnosis	Number of Studies of Resectability in Those With Disease Not Staged
MDCT angiography with 3D reconstruction vs. MDCT angiography without 3D reconstruction	0	1
MDCT vs. EUS-FNA	3	1
MDCT vs. MRI	7	2
MDCT vs. PET/CT	6	0
EUS-FNA vs. PET/CT	1	0
MRI vs. PET/CT	1	0

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; PET/CT = position emission tomography–computed tomography

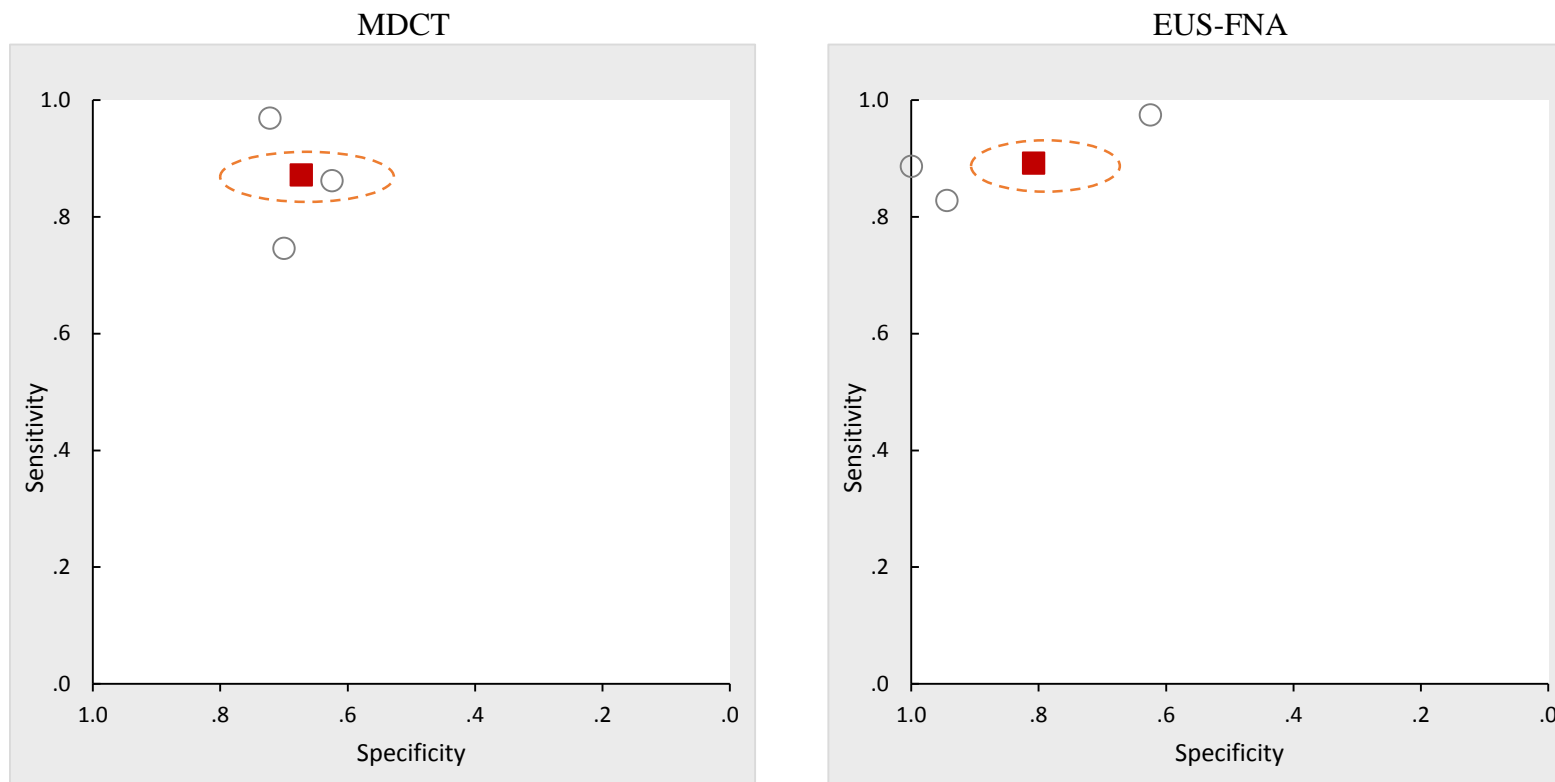
MDCT Angiography With 3D Reconstruction Versus Without 3D Reconstruction

One study²¹ addressed MDCT angiography with or without 3D reconstruction, and the study reported comparative accuracy in assessing resectability among patients with unstaged disease. The study was judged as low risk of bias. However, the study was performed by the developers of the 3D reconstruction software under consideration. We performed a statistical comparison of the sensitivity of MDCT without 3D reconstruction (89%; 95% CI, 68% to 97%) to the sensitivity of MDCT with 3D reconstruction (100%; 95% CI, 83% to 100%), and found no statistically significant difference, and we judged the evidence too imprecise to permit a conclusion. However, for detecting resectability, MDCT with 3D reconstruction (100%; 95% CI, 91% to 100%) was more accurate than MDCT without 3D reconstruction (79%; 95% CI, 64% to 89%); the rate differences were statistically significant. This means that, among patients whose disease was truly resectable, MDCT with 3D reconstruction identified a greater percentage as resectable than did MDCT without 3D reconstruction (the reference standard was the findings of an intraoperative exam). However, the potential for reporting bias (the authors may have published the article only because results favored their technology) and unknown consistency (i.e., there was only one study of this comparison) mean the evidence is insufficient to permit a general conclusion about comparative accuracy.

MDCT Versus EUS-FNA

Three studies⁵⁸⁻⁶⁰ compared MDCT versus EUS-FNA with respect to diagnostic accuracy. Two were judged as having moderate risk of bias, and one was judged as low risk of bias. We performed a meta-analysis of the three studies (see Figure 3) and found summary sensitivities for MDCT and EUS-FNA of 87 percent (95% CI, 82% to 91%) and 89 percent (95% CI, 85% to 93%), respectively, and we found summary specificities of 67 percent (95% CI, 53% to 78%) and 81 percent (95% CI, 68% to 90%). This evidence suggests a slight advantage of EUS-FNA, however statistical tests revealed no statistically significant differences, and we judged the evidence as too imprecise to permit a conclusion of similar accuracy (particularly notable was the uncertainty around specificities). Thus, we drew no conclusion.

Figure 3. ROC plot of diagnostic accuracy, MDCT versus EUS-FNA



The left side of the plot shows the multidetector computed tomography (MDCT) data in receiver operating characteristic (ROC) space; the right side shows the endoscopic ultrasound with fine-needle aspiration (EUS-FNA) data in ROC space. Each study contributed one circle to each side of the plot. The filled square shows the summary estimate, and the dashed region shows the 95% confidence interval range around the summary estimate.

One study⁵⁸ compared MDCT and EUS-FNA for the assessment of resectability in those with disease not staged. The study was judged to have low risk of bias, and it found similar accuracy for the two technologies (truly unresectable patients were correctly deemed unresectable at rates of 64% and 68% for MDCT and EUS-FNA, respectively; and patients with truly resectable disease were correctly deemed resectable at rates of 92% and 88% for MDCT and EUS-FNA, respectively). We judged the study to be sufficiently precise to permit a conclusion of similar accuracy. However, consistency was unknown, which limits the confidence one can have in the conclusion.

Based on the study's prevalence of unresectability of 53 percent, the results can be interpreted as follows: those whose disease is deemed unresectable by either MDCT or EUS-FNA have about an 88 percent chance of their disease actually being unresectable (positive predictive value), and those whose disease is deemed resectable by either test have about a 70 percent chance of their disease actually being resectable (negative predictive value). Translated to raw numbers, consider a hypothetical example in which there are 1,000 patients being assessed for resectability, and 397 are deemed unresectable by the imaging test. About 88 percent of these patients, or 350 patients, would be truly be unresectable and would avoid unnecessary surgery (if the decision were based only on the test result). The other 47 patients would not undergo resection since the imaging test suggested unresectability (again simplistically assuming the resectability decision was based only on the test result). An additional 603 patients would be deemed resectable by the imaging tests, and about 70 percent of them would actually be resectable (423 patients) and therefore would have successful surgery, and the other 30 percent (180 patients) would undergo unsuccessful surgery. All of these hypothetical numbers are based on the findings of a single study, and they assume that the prevalence of unresectability is 53 percent.

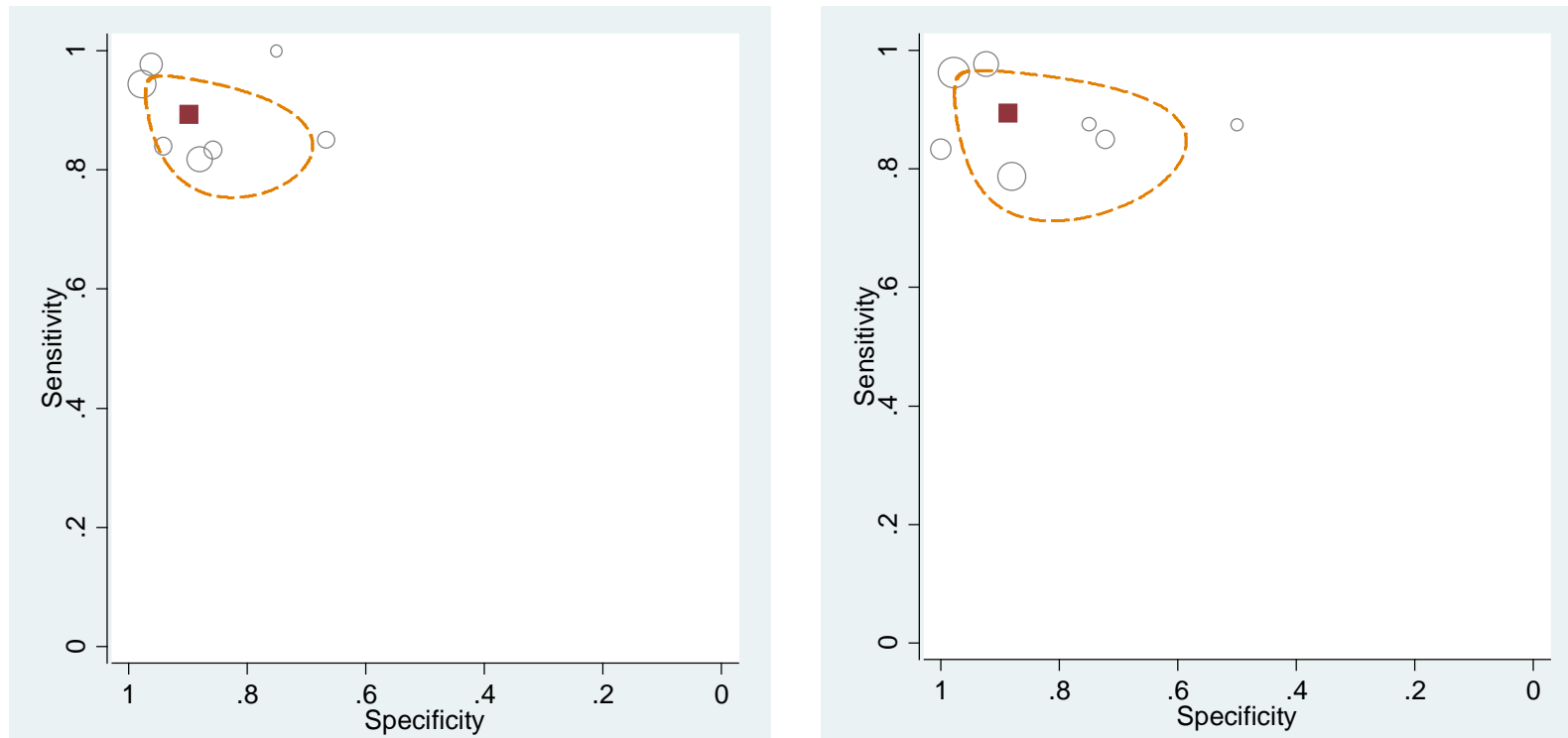
MDCT Versus MRI

Seven studies⁶¹⁻⁶⁷ compared MDCT and MRI with respect to diagnostic accuracy. Four⁶²⁻⁶⁵ were low risk of bias, and three^{61,66,67} were moderate risk of bias. Our meta-analysis found summary sensitivities of 89 percent for both technologies (95% CIs of 82% to 94% for MDCT and 81% to 91% for MRI), and summary specificities of 90 percent for MDCT (95% CI, 80% to 95%) and 89 percent for MRI (95% CI, 74% to 95%). These data we judged sufficiently precise to indicate similar accuracy. Plots in receiver operating characteristic (ROC) space appear in Figure 4 below. These plots show the similarity in accuracy between MDCT and MRI, with the filled squares in the same location of the plot, and the dashed area of 95 percent confidence slightly larger for MRI but with similar shapes and locations. The heterogeneity was lower for MDCT than EUS-FNA, and also was generally lower for sensitivity than specificity (tau=0.47 and 0.8 for MDCT sensitivity and MDCT specificity, respectively, as compared with tau=0.6 and 1.1 for EUS-FNA sensitivity and EUS-FNA specificity, respectively.)

To aid interpretation, we provide estimates for both positive predictive value (PPV) and negative predictive value (NPV). The median prevalence in the seven studies was 53 percent, and based on that prevalence, we estimate a PPV of 90 percent and an NPV of 88 percent. This means that a patient with a positive test result (on either MDCT or MRI) has approximately a 90 percent chance of having pancreatic adenocarcinoma, whereas a patient with a negative test result (on either MDCT or MRI) has only a 12 percent chance of having pancreatic adenocarcinoma.

Translated to raw numbers, considerable a hypothetical example in which there are 1,000 patients being diagnosed, and 521 test positive for pancreatic adenocarcinoma. About 90 percent of these patients, or 472 patients, would truly have the disease. The other 49 patients would be false alarms. An additional 479 patients would have tested negative, but only 421 of these would actually be negative for pancreatic adenocarcinoma. The other 58 of them (12 percent of 479) would be missed pancreatic adenocarcinomas. All of these hypothetical numbers are based on our meta-analytic summary sensitivity and specificity as well as an assumed prevalence of 53 percent.

Figure 4. ROC plot of diagnostic accuracy, MDCT versus MRI



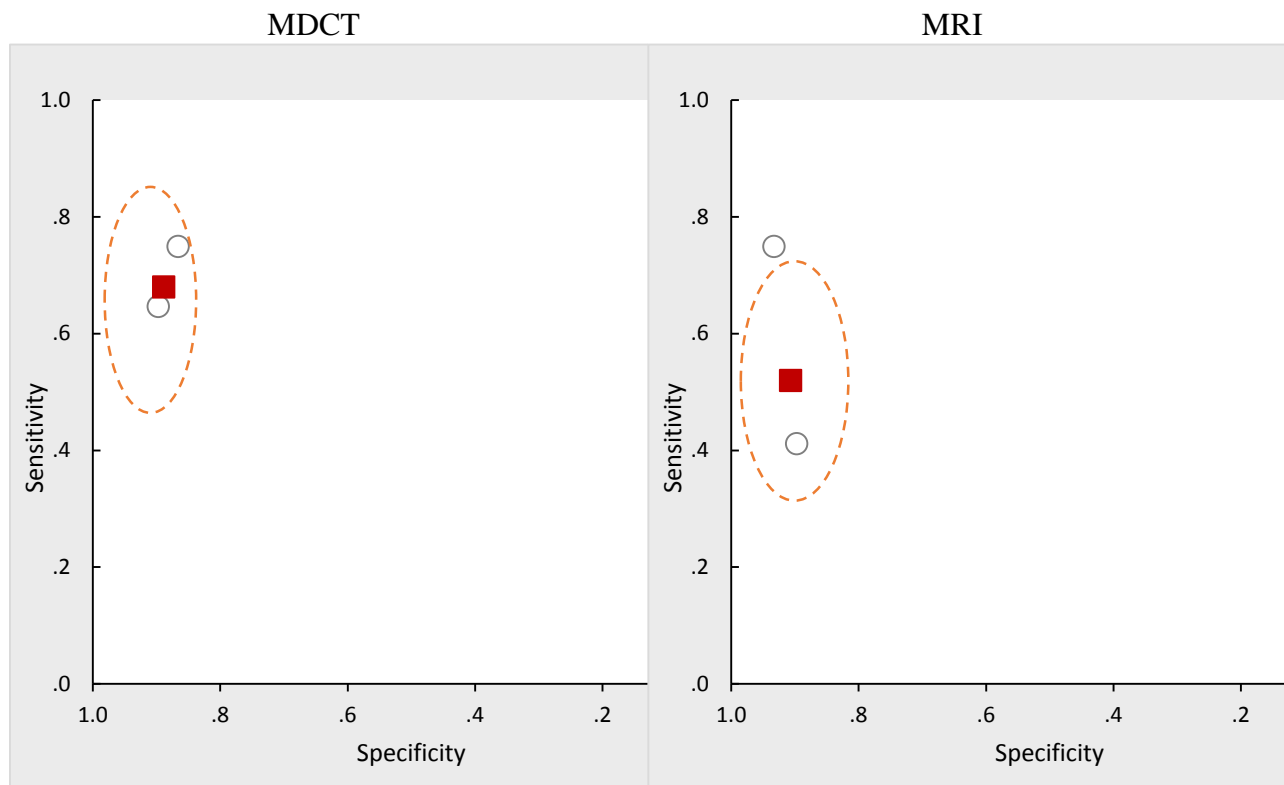
The left side of the plot shows the multidetector computed tomography (MDCT) data in receiver operating characteristic (ROC) space; the right side shows the magnetic resonance imaging (MRI) data in ROC space. Each study contributed one circle to each side of the plot. The filled square shows the summary estimate, and the dashed region shows the 95% confidence interval range around the summary estimate.

We also performed 35 sensitivity analyses of this meta-analysis (Appendix E). Four of the seven studies reported data for multiple readers separately; the above analysis used only reader #1 from these four studies. The sensitivity analysis all found very similar results regardless of which permutation of readers we used (see all estimates in Appendix E).

For the above meta-analysis of seven studies, we also measured the correlation between the end date of patient recruitment (i.e., the month when the last patient was enrolled in the study) and the difference in logit sensitivities. To enable this, we needed the end month of patient recruitment for all seven studies, but only five reported this information, so we assumed that the end of enrollment had occurred 2.3 years before the study publication month (2.3 years was the average for all studies). This correlation of seven studies' results did not reveal a convincing trend. The results for sensitivity showed an association ($R^2=0.78$) suggesting that later studies favored MRI over MDCT for diagnosis, but examination of the graph suggested that the finding was being driven by a single study (the year-2000 study), and when it was removed, the R^2 for the remaining six studies reduced to 0.26. For specificity, no correlation was apparent ($R^2=0.11$).

Two studies^{64,68} compared MDCT and MRI for the assessment of resectability in patients with disease not staged; both were judged low risk of bias. Our meta-analysis of the two studies (see Figure 5) yielded summary sensitivities for MDCT and MRI of 68 percent (95% CI, 47% to 85%) and 52 percent (95% CI, 31% to 72%), respectively, and we found summary specificities of 89 percent (95% CI, 77% to 96%) and 91 percent (95% CI, 80% to 97%). These suggest neither an advantage of MDCT nor an advantage of MRI (statistical tests not significant), and we judged the data too imprecise to indicate equivalence, thus we drew no conclusion.

Figure 5. ROC plot of resectability in those not staged, MDCT versus MRI



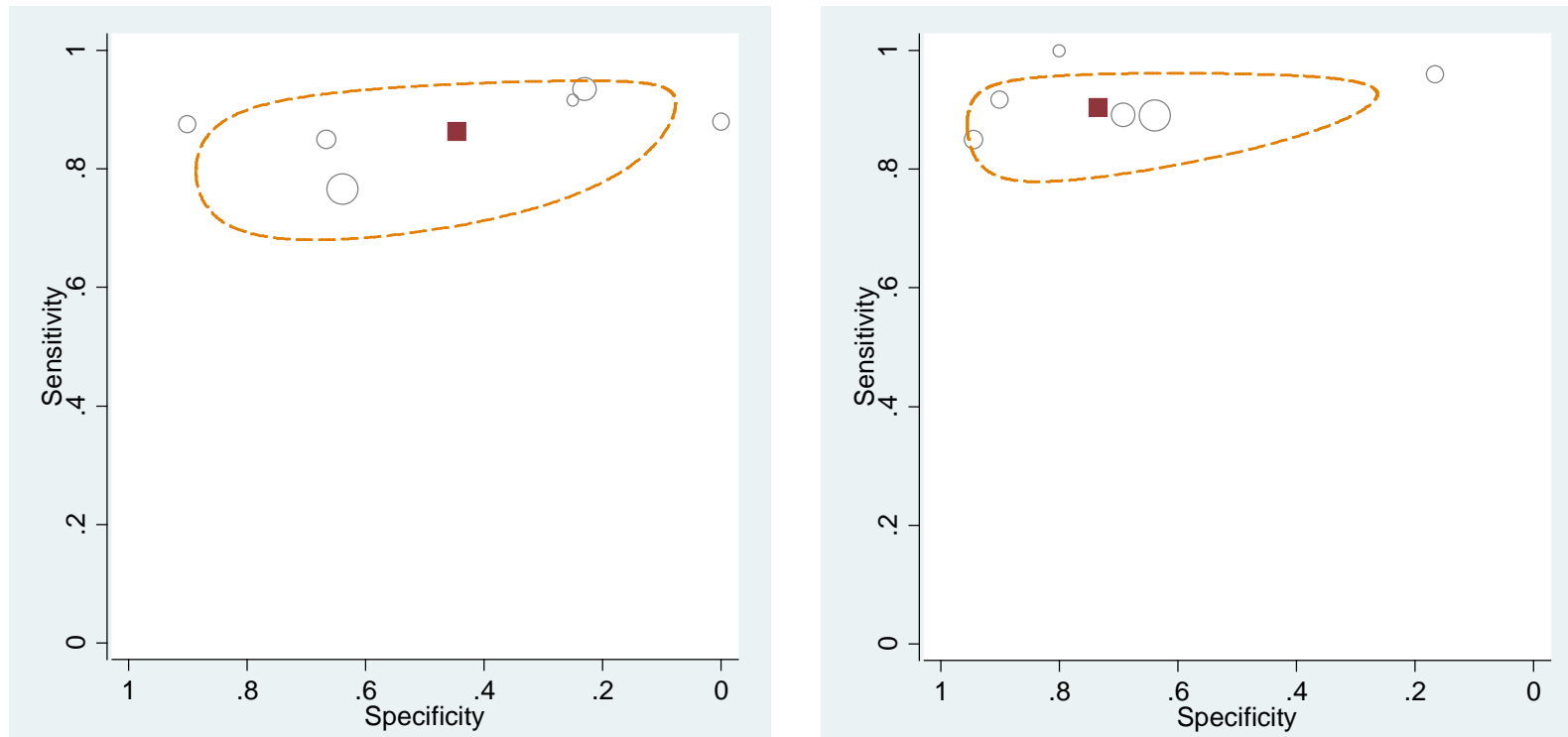
The left side of the plot shows the multidetector computed tomography (MDCT) data in receiver operating characteristic (ROC) space; the right side shows the magnetic resonance imaging (MRI) data in ROC space. Each study contributed one circle to each side of the plot. The filled square shows the summary estimate, and the dashed region shows the 95% confidence interval range around the summary estimate.

MDCT Versus PET/CT

Six studies^{65,69-73} compared MDCT and PET/CT with respect to diagnostic accuracy. Two^{65,71} were low risk of bias, and four^{69,70,72,73} were moderate risk of bias. Our meta-analysis found summary sensitivities of 85 percent (95% CI, 80% to 90%) for MDCT and 91 percent (95% CI, 85% to 94%) for PET/CT, and summary specificities of 55 percent for MDCT (95% CI, 44% to 66%) and 72 percent for PET/CT (95% CI, 61% to 81%). Statistical tests showed no clear difference for sensitivity, but also no statistical difference for either sensitivity or specificity.

Plots in ROC space appear in Figure 6 below. These plots show large uncertainty around specificity estimates (horizontal ovals), and this uncertainty explains why the apparent specificity difference (55% for MDCT vs. 72% for PET/CT) was not statistically significant. The general uncertainty was mostly due to the heterogeneity among different studies (rather than small sample sizes), with tau values of logit specificity of 0.75 for MDCT and 1.09 for PET/CT. The corresponding heterogeneity values for sensitivity (0.38 for MDCT and 0.21 for PET/CT) indicate higher consistency among study results for detecting pancreatic adenocarcinoma. Overall, given the wide uncertainty (caused by inconsistency among study results, particularly in the ability of these tests to rule out pancreatic adenocarcinoma), we drew no conclusion about this comparison.

Figure 6. ROC plot of diagnostic accuracy, MDCT versus PET/CT



The left side of the plot shows the multidetector computed tomography (MDCT) data in receiver operating characteristic (ROC) space; the right side shows the positron emission tomography–computed tomography (PET/CT) data in ROC space. Each study contributed one point to each side of the plot. The filled square shows the summary estimate, and the dashed region shows the 95% confidence interval range around the summary estimate.

For the above meta-analysis of six studies, we also measured the correlation between the end date of patient recruitment and the difference in logit sensitivities. This correlation did not reveal any trend ($R^2=0.03$ for both sensitivity and specificity).

EUS-FNA Versus PET/CT

One study⁷⁴ compared EUS-FNA and PET/CT with respect to diagnostic accuracy; we judged its risk of bias as moderate. Results statistically favored neither technology for either sensitivity (EUS-FNA, 81%; 95% CI, 62% to 91%; vs. PET/CT, 89%; 95% CI, 72% to 96%) or specificity (EUS-FNA, 84%; 95% CI, 62% to 94%, vs. PET/CT, 74%; 95% CI, 51% to 88%). Furthermore, we judged the evidence too imprecise to conclude similar accuracy. Thus, no conclusion is warranted.

MRI Versus PET/CT

One study⁷⁵ compared MRI and PET/CT with respect to diagnostic accuracy; we judged its risk of bias as low. Results statistically favored neither technology for either sensitivity (MRI, 85%; with 95% CI, 64% to 95%; vs. PET/CT, 85%; 95% CI, 64% to 95%) or specificity (MRI, 72%; 95% CI, 49% to 87%; vs. PET/CT, 94%; 95% CI, 74% to 99%). Furthermore, we judged the evidence too imprecise to conclude similar accuracy. Thus, no conclusion is warranted.

For other subquestions under KQ1(c through g), no included studies reported pertinent data.

Conclusions for KQ1

For single-test accuracy of diagnosis and resectability in patients with unstaged disease, we included nine systematic reviews, and drew the following conclusions:

- Evidence was insufficient to permit accuracy estimates for MDCT angiography with or without 3D reconstruction.
- For diagnosis using MDCT, one systematic review yielded a sensitivity estimate of 91 percent (95% CI, 86% to 94%) and a specificity estimate of 85 percent (95% CI, 76% to 91%). (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using EUS-FNA, three high-quality and recent systematic reviews yielded sensitivity estimates ranging from 83 percent to 92 percent and specificity estimates ranging from 95 percent to 100 percent. (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using MRI, three systematic reviews yielded sensitivity estimates of 84 percent to 85 percent and specificity estimates of 82 percent to 91 percent. (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using PET/CT, two systematic reviews yielded sensitivity estimates of 87 percent and 90 percent and specificity estimates of 83 percent and 90 percent. (Strength of evidence from published systematic reviews was not graded.)
- For MDCT, in assessing the resectability tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 81 percent (95% CI, 76% to 85%) and a specificity estimate of 82 percent (95% CI, 77% to 97%). (Strength of evidence from published systematic reviews was not graded.)
- For MRI, in assessing the resectability of tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 82 percent (95% CI, 69% to 91%) and a specificity estimate of 78 percent (95% CI, 63% to 87%). (Strength of evidence from published systematic reviews was not graded.)

For comparative test accuracy of diagnosis and resectability in patients with unstaged disease, our assessments of the evidence are summarized in Table 6 below. Of the eight sets of evidence listed in the table, we deemed five insufficient to permit conclusions because of imprecision. A sixth was insufficient because of the existence of only a single study and the possibility of publication bias. The other two rows represent our conclusions for KQ1b:

- MDCT and EUS-FNA have similar accuracy in the assessment of resectability of pancreatic adenocarcinoma in symptomatic adults with unstaged disease (Strength of evidence: low)
- MDCT and MRI have similar accuracy in the diagnosis of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate)

Table 6. Summary of evidence on KQ1b

Comparison	Clinical Decision	# Studies	Study Limitations	Direct-ness	Consistency	Precision	Reporting Bias	Strength of Evidence	Conclusion
MDCT angiography without 3D reconstruction vs. with 3D reconstruction	Resectability in those with unstaged disease	1 ²¹ (Total N=57)	Low	Direct	Unknown	Precise	Yes	Insufficient	NA
MDCT vs. EUS-FNA	Diagnosis	3 ⁵⁸⁻⁶⁰ (Total N=302)	Moderate	Direct	Inconsistent	Imprecise	No	Insufficient	NA
MDCT vs. EUS-FNA	Resectability in those not staged	1 ⁵⁸ (Total N=53)	Low	Direct	Unknown	Precise	No	Low	Similar accuracy
MDCT vs. MRI	Diagnosis	7 ⁶¹⁻⁶⁷ (Total N=397)	Moderate	Direct	Consistent	Precise	No	Moderate	Similar accuracy
MDCT vs. MRI	Resectability in those not staged	2 ^{64,68} (Total N=79)	Low	Direct	Consistent	Imprecise	No	Insufficient	NA
MDCT vs. PET/CT	Diagnosis	6 ^{65,69-73} (Total =278)	Moderate	Direct	Consistent	Imprecise	No	Insufficient	NA
EUS-FNA vs. PET/CT	Diagnosis	1 ⁷⁴ (Total N=45)	Moderate	Direct	Unknown	Imprecise	No	Insufficient	NA
MRI vs. PET/CT	Diagnosis	1 ⁶⁵ (Total N=38)	Low	Direct	Unknown	Imprecise	No	Insufficient	NA

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; NA = not applicable; PET/CT = positron emission tomography-computed tomography.

Test Performance of Imaging Modalities for Staging

KQ2: Comparative Effectiveness of Imaging Techniques for Staging

KQ2a. What is the staging accuracy of each imaging technique (for tumor size, lymph node status, vessel involvement, metastases, stage I–IV, and resectability)?

Key Points

- Two low-quality systematic reviews reported on CT for assessing vascular invasion. Both concluded that sensitivity and specificity were worse for the subset of studies using older or single-slice CT scanners than for the studies using newer multi-slice CT. Summary sensitivity values for the newer scanners ranged from 80 percent to 85 percent while summary specificity ranged from 82 percent to 97 percent. The evidence base in both reviews was small: four or five studies each. (Strength of evidence from published systematic reviews was not graded.)
- One low-quality systematic review reported on MR for assessing vascular invasion, concluding it had sensitivity of 63 percent and specificity of 93 percent. The evidence base was only four studies. (Strength of evidence from published systematic reviews was not graded.)
- One review of PET/CT included only a single study, which had reported 82 percent sensitivity and 97 percent specificity for detecting liver metastasis. (Strength of evidence from published systematic reviews was not graded.)

Detailed Synthesis

We included three reviews for this subquestion; none were high quality.^{51,56,76} No reviews reported on the ability of these imaging modalities to assess overall stage (I–IV) or TNM (tumor, lymph node, metastasis) components of staging.

Two reviews addressed the diagnosis of vascular invasion (Table 7): both included CT results and one also reviewed MRI data. Zhao (2009) analyzed CT (5 studies, 452 patients excluding single-slice CT studies) and provided separate analyses of the full set of CT studies and a subset of studies that used multi-slice scanners.⁵¹ Sensitivity was considerably higher for the later studies than for the rest, with no corresponding loss of specificity. The review of MRI⁷⁶ found only four studies (total 143 patients) and thus had a large uncertainty in its results.

A review of PET for pancreatic cancer staging⁵⁶ also tabulated a subset of studies using integrated PET/CT scanners. It found only one such study, which reported on only 50 patients (Table 8 and Table 9)

Table 7. KQ2a: Summary results of systematic reviews on vascular invasion

Modality	EUS-FNA	CT	MRI	PET/CT
Number of reviews	0	2	1	0
Quality of reviews	—	Low	Low	—
Most recent review	—	2013	2013	—
Range of results	—	Sensitivity: 73%-85% Specificity: 82%-95%	Sensitivity: 63% Specificity: 93%	—

CT = Computed tomography; EUS-FNA = endoscopic ultrasound with fine-needle aspiration;
MRI = magnetic resonance imaging; PET/CT = positron emission tomography–computed tomography.

Table 8. KQ2a: Summary results of systematic reviews on nodal metastasis

Modality	EUS-FNA	CT	MRI	PET/CT
Number of reviews	0	0	0	1
Quality of reviews	—	—	—	Low
Most recent review	—	—	—	2013
Range of results	—	—	—	No PET/CT studies answered this question

CT = Computed tomography; EUS-FNA = endoscopic ultrasound with fine-needle aspiration;
MRI = magnetic resonance imaging; PET/CT = positron emission tomography–computed tomography.

Table 9. KQ2a: Summary results of systematic reviews on liver metastasis

Modality	EUS-FNA	CT	MRI	PET/CT
Number of reviews	0	0	0	1
Quality of reviews	—	—	—	Low
Most recent review	—	—	—	2013
Range of results	—	—	—	Sensitivity 82% Specificity: 97%

CT = Computed tomography; EUS-FNA = endoscopic ultrasound with fine-needle aspiration;
MRI = magnetic resonance imaging; PET/CT = positron emission tomography–computed tomography.

Comparative Test Performance of Imaging Modalities for Staging

KQ2b. What is the comparative staging accuracy of the different imaging techniques?

Key Points

- EUS-FNA is more accurate than MDCT in the assessment of the T stage of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: low).
- MDCT and MRI have similar accuracy in the assessment of the vessel involvement of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate).
- PET/CT is more accurate than MDCT in the assessment of distant metastases of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: low).
- For all other test comparisons involving staging and the assessment of resectability in patients with staged disease, we deemed the evidence insufficient to permit conclusions, and the most common reason for insufficiency was imprecision.

Detailed Synthesis

For an overview of the studies included for comparative accuracy, including study locations and patient characteristics, see the section Key Question1b above entitled “Comparative Test Performance of Imaging Modalities for Diagnosis.” This section is divided into subsections based on the comparisons made by included studies (listed in Table 10 below).

Table 10. KQ2b: Numbers of studies comparing different tests for staging and resectability in staged patients

Comparison	Number of Studies of T Staging	Number of Studies of N Staging	Number of Studies of M Staging	Number of Studies of Precise Stage	Number of Studies of Vessel Involvement	Number of Studies of Resectability in Those Staged
MDCT vs. EUS-FNA	1	0	0	0	1	0
MDCT vs. MRI	1	1	5	1	3	1
MDCT vs. PET/CT	0	1	2	0	0	0
EUS-FNA vs. MRI	0	0	0	1	0	0
MRI vs. PET/CT	0	0	1	0	0	0

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration; M = metastasis; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; N = nodal; PET/CT = positron emission tomography–computed tomography; T = tumor.

MDCT Versus EUS-FNA

One study⁵⁸ compared MDCT and EUS-FNA with respect to T staging. Authors reported the data as the percentages of patients whose disease was accurately staged (41% by MDCT, vs. 67% by EUS-FNA), the percentage whose disease was overstaged (14% by MDCT, 18% by EUS-FNA), and the percentage whose disease was understaged (44% by MDCT, and 14% by EUS-FNA). (The reference standard was based on intraoperative findings.) The difference in accuracy was statistically significant by an exact McNemar’s test for paired binary data (our odds ratio for paired binary data also indicated statistical significance). However, consistency was unknown, which limits the confidence one can have in the conclusion.

One study⁷⁷ compared MDCT with EUS-FNA for the assessment of vessel involvement. Results statistically favored neither technology for either sensitivity (MDCT 56%; 95% CI, 34% to 75%; vs. EUS-FNA, 61%; 95% CI, 39% to 80%) or specificity (MDCT, 94%; 95% CI, 80% to 98%; vs. EUS-FNA, 91%; 95% CI, 76% to 97%). Furthermore, we judged the evidence too imprecise to conclude similar accuracy. Thus, no conclusion is warranted.

MDCT Versus MRI

One study⁷⁸ compared MDCT and MRI with respect to T staging. MDCT yielded an accurate T stage in 73 percent, whereas MRI yielded an accurate stage in 62 percent. This result was not statistically significant by the odds ratio for paired binary data, and also was not indicative of equivalence (95% confidence interval 0.93 to 2.9), so we drew no conclusion.

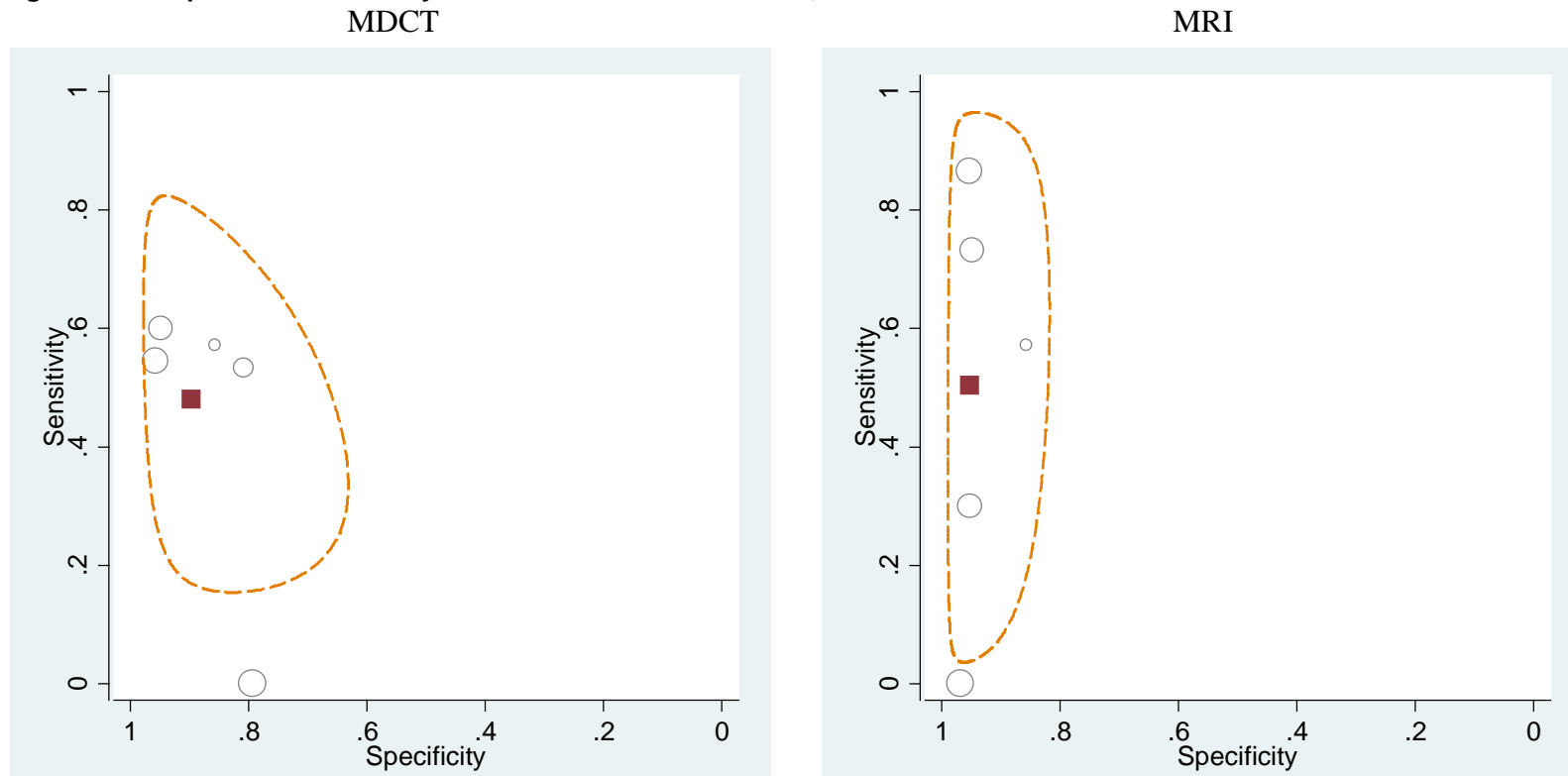
One study⁷⁸ compared these technologies with respect to N staging. Results statistically favored neither technology for either sensitivity (MDCT, 38%; 95% CI, 21% to 57%; vs. MRI, 15%; 95% CI, 5% to 36%) or specificity (MDCT, 79%; 95% CI, 63% to 90%; vs. MRI, 93%; 95% CI, 78% to 98%). Furthermore, we judged the evidence too imprecise to conclude similar accuracy. Thus, no conclusion is warranted.

Five studies^{63,65,78-80} compared these technologies with respect to the assessment of metastases. Our meta-analysis yielded sensitivity estimates of 48 percent (95% CI, 31% to 66%)

and 50 percent (95% CI, 19% to 81%) for MDCT and MRI, respectively. For specificity, the meta-analytic estimates were 90 percent (95% CI, 81% to 95%) and 95 percent (95% CI 91% to 98%) for MDCT and MRI, respectively. The comparisons were not statistically significant and we judged them as too imprecise to indicate equivalence, thus we drew no conclusion.

Plots in ROC space appear in Figure 7 below representing the five studies for assessment of metastases. The wide variability in sensitivity is shown graphically by the vertically shaped ovals, and the generally high specificity is shown by the fact that the ovals are on the left side of the ROC plot. Heterogeneity was low for MDCT (tau 0.50 for sensitivity and 0.53 for specificity) and MRI specificity (tau 0.14), but large for MRI sensitivity (tau 1.03). This latter value was caused by the five studies' sensitivity estimates encompassing most of the 0 percent to 100 percent scale (sensitivities of MRI of 87%, 73%, 57%, 30%, and 0% in the five studies). The study⁸⁰ that had found 0 percent sensitivity for both tests had investigated paraaortic lymph node metastases, which may be relatively hard to detect, thereby yielding such low values.

Figure 7. ROC plot of the accuracy of assessment of metastases, MDCT versus MRI



The left side of the plot shows the multidetector computed tomography (MDCT) data in receiver operating characteristic (ROC) space; the right side shows the positron emission tomography-computed tomography (PET/CT) data in ROC space. Each study contributed one point to each side of the plot.

We also performed two sensitivity analyses of this meta-analysis (see Appendix E). One of the five studies had reported data for three readers separately; the above analysis used only reader #1 from that study. The sensitivity analyses all found very similar results regardless of which reader we used (see all estimates in Appendix E).

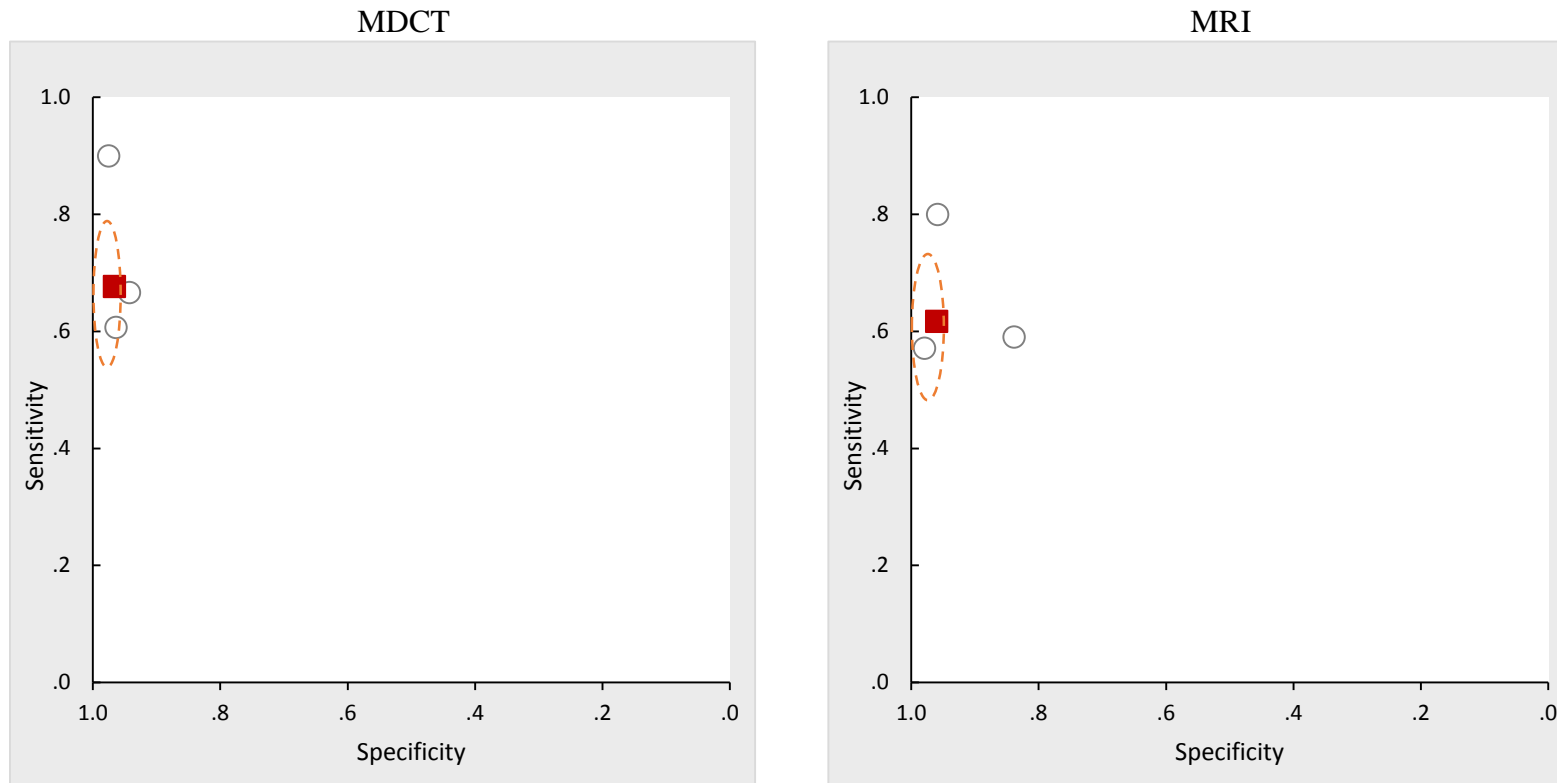
For the above meta-analysis of five studies, we also measured the correlation between the end date of patient recruitment and the difference in logit sensitivities. To enable this, we needed the end month of patient recruitment for all five studies, but only four reported this information, so we assumed that the end of enrollment had occurred 2.3 years before the study publication month (2.3 was the average for all studies). This correlation of five studies' results did not reveal a convincing trend. The results for sensitivity showed an association ($R^2=0.58$) suggesting that later studies favored MRI over MDCT for assessing metastases, but examination of the graph suggested that the finding was being driven by a single study (the year-2004 study),⁷⁸ and when it was removed, the R^2 for the remaining six studies reduced to 0.17. For specificity, no correlation was apparent ($R^2=0.16$).

One study⁷⁸ compared MDCT and MRI for the assessment of precise stage. MDCT was accurate in 46 percent and MRI was accurate in 36 percent; this difference was not statistically significant by the odds ratio for paired binary data, and furthermore the data were too imprecise to indicate equivalence (95 percent confidence interval 0.88 to 2.6).

Three studies^{64,68,78} compared these technologies for the assessment of vessel involvement (two were low risk of bias, and one was moderate risk of bias). The data are shown in Figure 8. The meta-analysis found similar accuracy (sensitivity 68% for MDCT with 95% CI, 55% to 79%; and 62% for MRI with 95% CI, 48% to 74%; specificity 97% for MDCT with 95% CI, 94% to 98%; and 96% for MRI with 95% CI 93% to 98%). Given the relatively wide confidence intervals, as well as the fact that there were only three studies, we deemed the evidence imprecise. Overall, we judged this as moderate evidence for concluding equivalent accuracy. Given the median prevalence of 13 percent, we computed a positive predictive value of 73%, and a negative predictive value of 5%.

Translated to raw numbers, consider a hypothetical example in which there are 1,000 patients being assessed for vessel involvement, and 114 test positive. About 73 percent of these patients, or 85 patients, would truly have vessel involvement. The other 29 patients would be false alarms. An additional 886 patients would have tested negative for vessel involvement, and almost all of these (95% or 840 patients) would actually be negative. The other 46 of them (5 percent of 886) would have undetected vessel involvement. All of these hypothetical numbers are based on our meta-analytic summary sensitivity and specificity as well as an assumed prevalence of 13 percent.

Figure 8. ROC plot of vessel involvement, MDCT versus MRI



The left side of the plot shows the multidetector computed tomography (MDCT) data in receiver operating characteristic (ROC) space; the right side shows the magnetic resonance imaging (MRI) data in ROC space. Each study contributed one circle to each side of the plot. The filled square shows the summary estimate, and the dashed region shows the 95% confidence interval range around the summary estimate.

One study⁷⁸ compared these technologies for assessing resectability in those with staged disease. Results statistically favored neither technology for sensitivity (MDCT, 67% with 95% CI, 48% to 81%; vs. MRI, 57% with 95% CI, 37% to 74%) or specificity (MDCT, 97% with 95% CI, 84% to 99%; vs. MRI, 90% with 95% CI, 74% to 96%). Furthermore, we judged the evidence too imprecise to conclude similar accuracy. Thus, no conclusion is warranted.

MDCT Versus PET/CT

One study⁷³ compared MDCT and PET/CT with respect to N staging. Study results suggested similar accuracy:

- MDCT sensitivity, 26 percent; 95 percent CI, 14 percent to 43 percent
- PET/CT sensitivity, 32 percent; 95 percent CI, 19 percent to 50 percent
- MDCT specificity, 75 percent; 95 percent CI, 50 percent to 90 percent
- PET/CT specificity, 75 percent; 95 percent CI, 50 percent to 90 percent

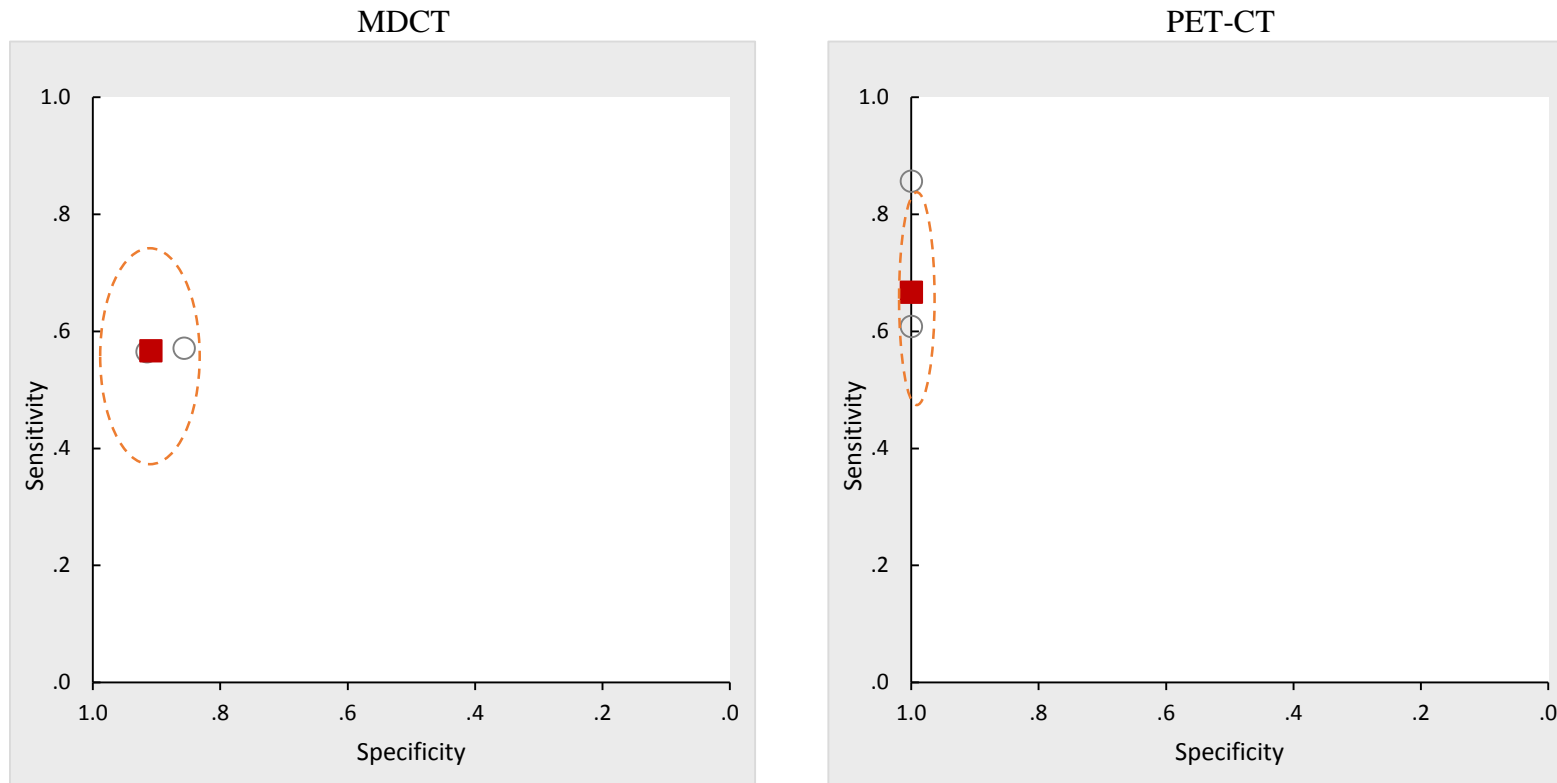
However, because it was only a single study, and it was at moderate risk of bias, we drew no conclusions.

Two studies^{65,81} compared these technologies with respect to the assessment of metastases. Neither study used dynamic IV contrast for PET-CT. The data are shown in Figure 9. Our meta-analysis yielded summary sensitivities of 57 percent (95% CI, 36% to 75%) and 67 percent (95% CI, 47% to 83%) for MDCT and PET/CT, respectively, and the summary specificities were 91 percent (95% CI 81% to 97%) and 100 percent (95% CI 95% to 100%) for MDCT and PET/CT, respectively. The difference in specificity was statistically significant in favor of PET/CT. The sensitivities were not statistically different, however, both studies slightly favored PET-CT. One⁶⁵ of the two studies was moderate risk of bias, and the other⁸¹ was low risk of bias, and we judged their results as consistent. Taken together, the evidence permits a conclusion that PET/CT is more accurate than MDCT in the assessment of metastases. PET/CT had 100% specificity in both studies, and neither study commented on possible reason(s) for these findings.

To help interpret the data, we note that the two studies had an average prevalence of metastases of 39 percent, and at this prevalence, a positive MDCT scan indicates an 80 percent chance of actually having metastases, whereas a positive PET/CT scan indicates a 100 percent chance. A negative MDCT scan indicates a 23 percent of having metastases, whereas a negative PET/CT scan indicates a 17 percent chance of having metastases.

Translated to raw numbers, considerable a hypothetical example in which there are 1,000 patients being assessed for metastases. 277 test positive on MDCT, 80 percent truly do have metastases (222 patients). By contrast, 261 test positive on PET-CT, and all of them truly do have metastases. Turning to negative tests, on MDCT 723 test negative, and 76 percent of them are truly negative (555 patients), with the other 168 patients (23 percent) having missed metastases. By contrast, 739 test negative on PET-CT, and 610 of them (83 percent) are truly negative, and the other 129 patients (17 percent) had missed metastases. All of these hypothetical numbers are based on our meta-analytic summary sensitivity and specificity as well as an assumed prevalence of 39 percent.

Figure 9. ROC plot of metastases, MDCT versus PET-CT



The left side of the plot shows the multidetector computed tomography (MDCT) data in receiver operating characteristic (ROC) space; the right side shows the positron emission tomography–computed tomography (PET-CT) data in ROC space. Each study contributed one circle to each side of the plot. The filled square shows the summary estimate, and the dashed region shows the 95% confidence interval range around the summary estimate.

EUS-FNA Versus MRI

One study⁸² compared EUS-FNA and MRI for the assessment of precise TNM stage. EUS-FNA provided an accurate stage in 71 percent of patients (34/48), whereas MRI did so in 75 percent (36/48). The matched pairs odds ratio was not statistically significant, and data were too imprecise to suggest equivalence (95 percent confidence 0.43 to 1.5). Thus, we drew no conclusion.

MRI Versus PET/CT

One study⁶⁵ compared MRI and PET/CT with respect to the assessment of metastases. One study compared these technologies with respect to N staging. Results statistically favored neither technology for either sensitivity (MDCT, 57%; 95% CI, 25% to 84%; vs. PET/CT, 86%; 95% CI, 48% to 97%) or specificity (MDCT, 86%; 95% CI, 48% to 97%; vs. PET/CT, 94%; 95% CI, 64% to 100%). Furthermore, we judged the evidence too imprecise to conclude similar accuracy. Thus, no conclusion is warranted.

For other subquestions under KQ2 (c through g), no included studies reported pertinent data.

Conclusions for KQ2

For single-test accuracy of staging and resectability in patients with staged disease, we included one low-quality systematic review published in 2009 that addressed this question, and assessed the accuracy of CT in assessing vascular involvement. When the review considered only studies published since 2004, the review estimated the sensitivity of CT to be 85 percent (95% CI, 78% to 91%) and specificity to be 82 percent (95% CI, 74% to 88%). We did not grade the strength of evidence from published systematic reviews.

For comparative test accuracy of staging and resectability in patients with staged disease, our assessments of the evidence are summarized in Table 11 below. Of the 12 sets of evidence listed in the table, we deemed 7 insufficient to permit conclusions due to imprecision. Two others were insufficient because of the existence of only a single study and a moderate risk of bias. The other three rows represent our conclusions for KQ2b:

- EUS-FNA is more accurate than MDCT in assessing the T stage of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: low)
- MDCT and MRI have similar accuracy in assessing the vessel involvement of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate)
- PET/CT is more accurate than MDCT in assessing metastases of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: low)

Table 11. Summary of evidence on KQ2b

Comparison	Clinical Decision	# Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence	Conclusion
MDCT vs. EUS-FNA	T staging	1 ⁵⁸ (Total N=49)	Low	Direct	Unknown	Precise	No	Low	Evidence favors EUS-FNA
MDCT vs. EUS-FNA	Vessel involvement	1 ⁷⁷ (Total N=50)	Moderate	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI	T staging	1 ⁷⁸ (Total N=59)	Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI	N staging	1 ⁷⁸ (Total N=58)	Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI	Metastases	5 ^{63,65,78-80} (Total N=232)	Low	Direct	Inconsistent	Imprecise	No	Insufficient	NA
MDCT vs. MRI	Precise stage	1 ⁷⁸ (Total N=59)	Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI	Vessel involvement	3 ^{64,68,78} (Total N=213)	Low	Direct	Consistent	Imprecise	No	Moderate	Similar accuracy
MDCT vs. MRI	Resectability in those staged	1 ⁷⁸ (Total N=59)	Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. PET/CT	N staging	1 ⁷³ (Total N=47)	Moderate	Direct	Unknown	Precise	No	Insufficient	NA
MDCT vs. PET/CT	Metastases	2 ^{65,81} (Total N=96)	Moderate	Direct	Consistent	Precise	No	Low	Evidence favors PET/CT
EUS-FNA vs. MRI	Precise stage	1 ⁸² (Total N=48)	Moderate	Direct	Unknown	Precise	No	Insufficient	NA
MRI vs. PET/CT	Metastases	1 ⁶⁵ (Total N=14)	Low	Direct	Unknown	Imprecise	No	Insufficient	NA

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration; M = metastasis; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; N = nodal; NA = not applicable; PET/CT = positron emission tomography–computed tomography; T = tumor

Harms of Imaging Modalities

KQ3: Harms of Imaging Techniques for Diagnosis and/or Staging

Key Points

- Procedural harms were reported in many EUS-FNA imaging studies, but not in many studies of the other imaging technologies.
- The most commonly reported procedural harms of EUS-FNA were pancreatitis (with rates ranging from 0% to 3.7%), postprocedural pain (0.1% to 2.0%), and bleeding/puncture/perforation (0% to 4.3%).

Detailed Synthesis

We included 78 studies for this key question. Fifty described harms due to imaging tests for the diagnosis/staging of pancreatic cancer and were published in the year 2000 or later, and the other 28 were not specific to pancreatic cancer and were published in the year 2009 or later. This later date was chosen given the anticipated large amount of studies addressing harms of imaging in patients with any indication for the procedures.

Pancreas-specific studies were published from 1991 to 2013, and studies evaluated as few as 50 patients⁸³ or as many as 1,034 patients.⁸⁴ One study by Eloubeidi et al. (2004)⁸⁵ contacted 27 EUS training centers in the United States to request information regarding total number of EUS-FNAs of solid pancreatic masses performed, the duration of time over which these procedures were performed, and cases of pancreatitis. Authors reported that patient-specific information was not provided, but self-reported episodes of acute pancreatitis were provided.⁸⁵ Settings included university hospitals, tertiary care medical centers, and cancer centers. Most studies enrolled patients suspected of pancreatic adenocarcinoma or patients with solid pancreatic lesions. The percentage of female patients ranged from 29 percent to 83 percent. Nonpancreas-specific studies were published from 2009 to 2013; one integrated retrospective analysis included trials conducted as early as 1993.⁸⁶ Studies evaluated as few as 1 patient or as many as 106,000 patients.⁸⁷ Settings included outpatient radiology centers, university hospitals, tertiary care medical centers, and cancer centers.

Below, the procedural harms data are discussed in separate sections for each imaging technology. Each technology's section is further divided into studies in which the imaging test was used specifically in the diagnosis and staging of pancreatic adenocarcinoma ("Harms studies specific to pancreatic cancer"), and other studies in which the imaging test was used for other purposes ("Recent harms studies not specific to pancreatic cancer").

MDCT

Harms Studies Specific to Pancreatic Cancer

Two MDCT studies reported adverse events.^{60,88} Sakamoto et al. (2008)⁸⁸ enrolled 119 patients suspected of having a pancreatic solid tumor because of abdominal screening findings on EUS-FNA or CT. The percentage of female patients was 39 percent and the mean age was 68.7 years. The study was conducted in Japan at Kinki University from March 2002 to August 2006. Three patients experienced an allergic eruption to the contrast agent (100 mL Optiray 320).

Agarwal et al. (2004)⁶⁰ enrolled patients with primary pancreatic neoplasm undergoing distal pancreatectomy and had no previous pancreatic resection or metastatic neoplasm. A total of 179 patients were included, and 114 were female. The mean age was 61 years, with a range of 19–86 years. The study was conducted in the United States at a cancer center between November 2000 and November 2001. Eighty-one of the enrolled patients underwent MDCT and two patients experienced postprocedural abdominal pain that completely subsided within 24 hours. The reported harms rate was 2.5 percent (2/81).

Recent Harms Studies Not Specific to Pancreatic Cancer

CT-related adverse events (range 0.13% to 61.5% [all moderate]) were evaluated in more than 180,497 patients in 12 studies.^{87,89-99} Most studies evaluated CT, however three studies evaluated CT and CT angiography^{91,92,97} and two studies evaluated CT coronary angiography.^{96,98} Eight studies included at-risk patients.^{89,90,92-96,98}

Non-ionic contrast agents, introduced in the 1970s, have a lower osmolarity than blood and are therefore less likely to cause adverse reactions.⁹⁹ Non-ionic contrast agents evaluated included iopromide,^{87,89,92,99} iomeprol,^{89,90,99} iohexol,^{89,90,97} iopamidol,^{90,91,96,98,99} iodixanol,^{89,98} and ioversol.^{90,94,99}

One study retrospectively reviewed extravasation (an inadvertent leakage of fluid from an intravenous site into the surrounding soft tissue) and allergic-like reactions from 24,826 injections (12,142 previously warmed) of intravenous (IV) iopamidol in CT and CT angiography examinations.⁹¹ The authors indicated that extrinsic warming (to 37 °C) appeared to affect adverse event rates for iopamidol 370 (8 events [warming] vs. 26 events [no warming]) but did not affect rates for iopamidol 300 (74 events [warming] vs. 69 events [no warming]).

Another study reported more delayed adverse reactions from iohexol (37/258) than controls (7/281).⁹⁷ Delayed adverse reactions are typically defined as occurring 1 hour or more after administration of a contrast medium.⁹⁷ In this report, Loh et al. reported statistically significantly more delayed adverse reactions (e.g., skin rashes, itching, headache) occurred with contrast-enhanced CT compared with controls. Kingston et al. (2012)⁹² focused on rates of extravasation in 26,854 patients. Results indicated that the “presence of cancer, hypertension, smoking and recent surgery was associated with higher extravasation rates.” Extravasations most commonly occurred at the elbow (71.4%).

Cadwallader et al. (2011)⁹⁵ reported results from 198 scans of at-risk patients to determine the risk of fatal cancer induction. Forty-one (20.7%) scans did not alter case management of the patient and were thus deemed as unnecessarily exposing patients to CT radiation. According to the National Cancer Institute, the extra risk of one person to develop a fatal cancer from a CT procedure is about 1 in 2,000.¹⁰⁰

Two studies reported only mild-to-moderate harms;^{89,98} two studies included at-risk patients.^{89,98} Six studies, however, reported serious/severe adverse events;^{87,90,93,94,96,99} five (42%) studies enrolled at-risk patients.^{90,93,94,96,99} Two studies reported 15 deaths within 45 days⁹³ after CT. Mitchell et al. (2012)⁹³ enrolled 633 patients; 174 undergoing computed tomography pulmonary angiography (CTPA) to exclude pulmonary embolism and 459 patients who did not undergo CTPA (non-CTPA). Study groups were similar for presumptive risk factors for contrast-induced nephropathy (CIN), such as anemia, diabetes mellitus, and history of hypertension and baseline renal insufficiency; however, significantly more CTPA patients had vascular disease (15% vs. 8%) and congestive heart failure (12% vs. 5%). Seventy patients (11%) developed CIN; slightly more were patients undergoing CTPA than patients without (14% vs. 10%). All-cause

45-day mortality rate was slightly higher in CTPA patients (3% vs. 2%) with 15 deaths during this time. Three patients undergoing CTPA went into severe renal failure, with two ultimately dying. The authors indicated that the “development of CIN was associated with an increased risk of death from any cause (relative risk = 12, 95 percent CI 3 to 53).”

Kobayashi et al. (2013)⁹⁰ reported 23 (0.06%) severe reactions including shock, hypotension, desaturation, and airway obstruction in a retrospective cohort study of 36,472 patients. Patients received various nonionic low-osmolar contrast agents; approximately half of the study population was diabetic (19.5%) or hypertensive (28.6%). Vogl et al. (2012)⁹⁴ reported anaphylactoid adverse reactions requiring hospitalization in 4 (0.03%) patients receiving ioversol. Of the 10,836 patients enrolled at 72 centers in Germany, more than 5,000 had 1–7 concomitant diseases, including diabetes mellitus and renal insufficiency. Jung et al (2102)⁹⁹ focused on cutaneous adverse reactions in 47,388 patients receiving various nonionic monomers such as iomeprol. Severe reactions such as severe generalized urticaria and facial edema occurred in 16 patients. The three remaining studies reported shortness of breath (5 patients)⁸⁷ and one case of atrial fibrillation (patient on peritoneal dialysis),⁹⁶ See Appendix C for details on CT-related adverse events in these studies.

EUS-FNA

Harms Studies Specific to Pancreatic Cancer

The four most commonly reported harms of EUS-FNA were pancreatitis; pain; perforation, puncture, or bleeding; and tumor seeding. Sixteen studies reported that there were no harms or complications resulting from EUS-FNA procedures.^{83,101-115}

Twenty-four studies reported pancreatitis as an adverse event.^{84,85,104,113,116-136} The number of patients at risk of pancreatitis ranged from 24 to 4,909, and the mean age range was 57–68.2 years. The range of rates reported for pancreatitis was 0 percent to 3.7 percent. Fifteen studies indicated patients experienced mild or acute pancreatitis,^{85,116,117,119-122,124,127-130,132,133,135} three studies reported moderate pancreatitis,^{84,116,125} and one study reported severe pancreatitis.⁸⁴ Eight did not specify whether pancreatitis was mild/acute, moderate, or severe.^{113,118,122,123,126,131,134,136} Table 12 below provides further details.

Table 12. Rates of pancreatitis after EUS-FNA

Study	Pancreatitis Details	Rate of Harm
Katanuma et al. 2013 ¹¹⁶	Moderate pancreatitis	0.3% (1/327)
Katanuma et al. 2013 ¹¹⁶	Mild pancreatitis	1.5% (5/327)
Lee et al. 2013 ¹¹⁸	Mild acute pancreatitis	2.4% (2/81)
Lee et al. 2013 ¹¹⁸	Pancreatitis	3.7% (7/188)
Ikezawa et al. 2012 ¹¹⁹	Mild pancreatitis treated conservatively	1.8% (1/56)
Siddiqui et al. 2012 ¹²⁰	Mild acute pancreatitis (resolved within 1 day)	0.3% (2/677)
Beane et al. 2011 ¹²¹	Acute pancreatitis requiring hospital admission and conservative treatment	1.1% (2/179)
Fisher et al. 2011 ¹³⁴	Pancreatitis	2.4% (4/170)
Iglesias-Garcia et al. 2011 ¹³³	Mild acute pancreatitis, requiring hospitalization for 4–5 days	1.1% (2/182)
Kopelman et al. 2011 ¹²²	Any morbidity other than mild pancreatitis	0% (0/102)
	Mild pancreatitis resolved spontaneously	1% (1/102)
Carrara et al. 2010 ⁸⁴	Moderate acute pancreatitis	0.1% (1/1034)
	Severe acute pancreatitis	0.1% (1/1034)

Table 12. Rates of pancreatitis after EUS-FNA (continued)

Study	Pancreatitis Details	Rate of Harm
Chang et al. 2009 ¹³⁶	"Clinical" pancreatitis (did not define "clinical")	0% (0/139)
Fisher et al. 2009 ¹²³	Pancreatitis	0% (0/93)
Yusuf et al. 2009 ¹³⁵	Mild pancreatitis	1.3% (11/842)
Eloubeidi et al. 2007 ^{124,137-141}	Major complication: acute pancreatitis	0.9% (5/547)
Mahnke et al. 2006 ¹²⁵	Moderate pancreatitis	0.3% (1/310)
Bournet et al. 2006 ¹²⁶	Pancreatitis	0.4% (1/224)
Mortensen et al. 2005 ¹²⁷	Acute pancreatitis	0.1% (1/670)
Ryozawa et al. 2005 ¹¹³	Pancreatitis	0% (0/52)
Eloubeidi et al. 2004 ⁸⁵	Acute pancreatitis	0.3% (14/4909)
Gress et al. 2002 ¹²⁸	Acute pancreatitis	2% (2/100)
Harewood and Wiersema 2002 ¹²⁹	Mild pancreatitis requiring 2-day hospital stay	0.5% (1/185)
Gress et al. 2001 ¹³¹	Pancreatitis	1% (1/102)
O'Toole et al. 2001 ¹³⁰	Acute pancreatitis	1.2% (3/248)
Voss et al. 2000 ¹³²	Acute pancreatitis	0% (0/99)

EUS-NFA = Endoscopic ultrasound with fine-needle aspiration.

Ten studies reported pain as an adverse event.^{88,116,120,123,124,132,142-145} The number of patients at risk of pain ranged from 28 to 677, and the mean age range was 62–66.5 years. The range of rates reported for pain was 0.1 percent to 2.0 percent. Six studies specifically mentioned the development of abdominal pain.^{88,120,124,132,143,145} Table 13 provides further details.

Table 13. Rates of pain after EUS-FNA

Study	Pain Details	Rate of Harm
Katanuma et al. 2013 ¹¹⁶	Mild abdominal pain	1.2% (4/327)
Siddiqui et al. 2012 ¹²⁰	Abdominal pain	0.1% (1/677)
Kliment et al. 2010 ¹⁴²	Minor pain treated with a single dose of analgesics	1% (2/207)
Fisher et al. 2009 ¹²³	Pain requiring hospital re-admission	1.1% (1/93)
Zamboni et al. 2009 ¹⁴⁴	Pain after the procedure, not clinically significant	1.1% (6/545)
Al-Haddad et al. 2008 ¹⁴⁵	Moderate abdominal pain requiring ER admission but no hospital stay and treated with oral analgesics	0.5% (1/210)
	Moderately severe abdominal pain within 2 hours, requiring hospital admission	1% (2/210)
Sakamoto et al. 2008 ⁸⁸	Abdominal pain, transient	2.0% (2/98)
Shah et al. 2008 ¹⁴³	Abdominal pain	1.6% (2/123)
Eloubeidi et al. 2007 ^{124,137-141}	Major complication: severe pain	0.5% (3/547)
	Minor complication: abdominal pain	0.9% (5/547)
Voss et al. 2000 ¹³²	Abdominal pain and pyrexia, resolved spontaneously	1% (1/99)

EUS-NFA = Endoscopic ultrasound with fine-needle aspiration.

Twenty studies reported perforation, puncture, or bleeding as an adverse event.^{84,88,113,116,118,120,123-127,131-134,142,143,146-149} We combined these three concepts because all three can be caused by endoscopic ultrasound and/or fine-needle aspiration, and studies may use different words to describe the event (e.g., a perforation that results in bleeding could be described by one study as perforation but by another study as bleeding). The number of patients at risk of perforation, puncture, or bleeding ranged from 52 to 1,034, and the mean age range was 47–68.2 years. The range of rates reported for this outcome was 0 percent to 4.3 percent. Table 14 provides further details.

Table 14. Rates of bleeding, perforation, or puncture after EUS-FNA

Study	Perforation/Puncture/Bleeding Details	Rate of Harm
Katanuma et al. 2013 ¹¹⁶	Mild bleeding	0.3% (1/327)
Lee et al. 2013 ¹¹⁸	Bleeding	3.2% (6/188)
Hayashi et al. 2013 ¹⁴⁶	Punctures resulting in peripancreatic abscess and requiring antibiotics	0.7% (1/138)
Ootaki et al. 2012 ¹⁴⁷	Self-limited bleeding during or after EUS-FNA (in conscious sedation group)	0.5% (2/371)
Siddiqui et al. 2012 ¹²⁰	Significant intra-procedural bleeding after FNA	0% (0/677)
	Bowel perforations	0% (0/677)
Fisher et al. 2011 ¹³⁴	Bleeding (self limited)	0% (0/170)
	Perforation	0.6% (1/170)
	Bile leak	0.6% (1/170)
Iglesias-Garcia et al. 2011 ¹³³	Bleeding at site of gastric puncture	0.5% (1/182)
Itoi et al. 2011 ¹⁴⁸	Procedure-related bleeding, treated by conservative therapy without blood transfusion	0.6% (2/356)
Carrara et al. 2010 ⁸⁴	Mild intracystic and retroperitoneal hemorrhage	0.1% (1/1034)
	Mild hemorrhage	0.1% (1/1034)
	Severe perforation/death	0.1% (1/1034)
	Mild endoductal hemorrhage	0.2% (2/1034)
	Mild intracystic hemorrhage	0.6% (6/1034)
Kliment et al. 2010 ¹⁴²	Minor bleeding without treatment necessary	1.5% (3/207)
Fisher et al. 2009 ¹²³	Perforation	0% (0/93)
	Minor mucosal bleeding requiring adrenaline injection	1.1% (1/93)
	Puncture of the superior mesenteric vein	1.1% (1/93)
	Mild self-limiting mucosal bleeding, stopped without intervention	4.3% (4/93)
Sakamoto et al. 2008 ⁸⁸	Bleeding from FNA site	0% (0/98)
Shah et al. 2008 ¹⁴³	Periduodenal bleeding	0.8% (1/123)
Eloubeidi et al. 2007 ^{124,137-141}	Minor complication: exaggerated bleeding	0.4% (2/547)
Rocca et al. 2007 ¹⁴⁹	Minor intracystic hemorrhage	0.3% (1/293)
Bournet et al. 2006 ¹²⁶	Upper gastrointestinal bleeding	0.4% (1/224)
	Perforation, duodenal	0.4% (1/224)
Mahnke et al. 2006 ¹²⁵	Mild bleeding	0.3% (1/310)
Mortensen et al. 2005 ¹²⁷	Massive gastrointestinal bleeding	0.1% (1/670)
Ryozawa et al. 2005 ¹¹³	Hemorrhage	0% (0/52)
	Perforation	0% (0/52)
Gress et al. 2001 ¹³¹	Substantial gastric mucosal bleeding with clot formation	2.0% (2/102)
Voss et al. 2000 ¹³²	Bleeding	4% (4/99)

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration.

Four studies^{88,103,104,113} specifically reported that tumor seeding after EUS-FNA had not occurred; these studies had enrolled a total of 418 patients. Additionally, other complications, such as infection, brief hypoxia, and reversal of medication, were reported. Five studies reported infection, with rates ranging from 0 percent to 6.7 percent.^{113,118,121,125,126} Two studies reported brief hypoxia,^{121,124} with rates ranging from 0.3 percent to 0.6 percent, and two studies reported reversal of medication usage,^{124,125} with rates ranging from 0.2 percent to 0.6 percent.

Recent Harms Studies Not Specific to Pancreatic Cancer

Katanuma et al. (2013)¹¹⁶ reported 11 harms (1 moderate) in 316 patients. In multivariate analysis, tumors measuring 20 mm or less in diameter (odds ratio [OR], 18.48; 95% CI, 3.55 to 96.17; p<0.001) and pancreatic neuroendocrine tumors (OR, 36.50; 95% CI, 1.73 to 771.83; p=0.021) were significant independent risk factors for post-procedural events.

EUS-related adverse events (range 0.06% to 14.4% [mostly minor] were reported in more than 21,088 patients in five studies.¹⁵⁰⁻¹⁵⁴ Two studies enrolled at-risk patients and focused on sedation-related complications.^{150,151} One study enrolled 799 patients (more than 60% classified as ASA Class III)¹⁵⁰ (see Appendix C for further details). In multivariate analysis, male sex (OR, 1.75; 95% CI, 1.08 to 2.85; p=0.02), ASA class 3 or more (OR, 1.90; 95% CI, 1.11 to 3.25; p=0.02), and body mass index (OR, 1.05; 95% CI, 1.01 to 1.09; p=0.009) were independent predictors of airway modifications. More than 65 percent of patients randomly assigned to midazolam/meperidine or propofol in another study were ASA Class III or higher (18% ASA Class IV).¹⁵¹ Of the 151 patients enrolled, 34 patients underwent EUS. No significant differences were reported in overall cardiopulmonary complication rates.

Forty-two (0.4%) serious adverse events were reported by Niv et al. (2011)¹⁵³ in a 7-year retrospective review of physician reporting. Harms from EUS-FNA and endoscopic retrograde cholangiopancreatography (ERCP) included perforation (69%), bleeding (4.8%), cardiovascular and respiratory (4.8%), teeth trauma (2.4%) and other (19%). “Critical outcomes” for the 42 patients involved included 15 deaths (35.7%) and 18 (42.9%) patients with residual damage. The incidence of mortality for EUS-related procedures (diagnostic and interventional) has reportedly varied between 0 percent and 0.06 percent.¹⁵² Eloubeidi et al. (2009)¹⁵⁴ reported cervical esophageal perforations in three (0.06%) patients at the time of endoscopic ultrasound intubation. One patient reported chest pains and two patients reported excessive salivation and sore throat prompting a physical exam. All patients underwent surgical repair and resumed swallowing without complications. Lastly, Kalaitzakis et al. (2011)¹⁵² reported 9 (0.2%) EUS-FNA related harms including desaturation, supraventricular tachycardia, and gallbladder and duodenal perforations. Jenssen et al. (2012) indicated that gastrointestinal perforations from EUS-FNA typically occurred either at areas of angulation, in the presence of unexpected anatomical alterations, or in luminal obstruction.¹⁵⁵

See Appendix C for details on EUS-FNA–related adverse events in these studies.

MRI

Harms Studies Specific to Pancreatic Cancer

No included studies reported procedural harms of MRI.

Recent Harms Studies Not Specific to Pancreatic Cancer

MRI-related adverse events (range 0% to 64.6%) were evaluated in more than 156,962 patients in 11 studies.^{86,87,156-164} Adverse events from contrast-enhanced MRIs were the focus of 10 (91%) studies.^{86,87,156-163} The following contrast agents were administered in nine studies:

- Gadobenate dimeglumine (Gd-BOPTA)¹⁵⁶
- Gadobutrol (Gd-BT-DO3A)^{86,156,159,163}
- Gadoterate meglumine (Gd-DOTA)^{158,161}
- Gadopentetate dimeglumine (Gd-DTPA)^{86,87}
- Gadodiamide (Gd-DTPA-BMA)⁸⁶
- Gadoversetamide (Gd-DTPA-BMEA)⁸⁶
- Gadoxetic acid disodium salt (Gd-EOB-DTPA)¹⁶⁰
- Gadoteridol (Gd-HP-DO3A)⁸⁶
- Manganese chloride tetrahydrate (CMC-001)¹⁵⁷
- Oral manganese (MnCl₂)¹⁶²

See Appendix C for a list of currently marketed gadolinium [GD] agents for MRI. Contrast-enhanced MRIs, widely used for more than 20 years, provide increased sensitivity and specificity of lesion detection.¹⁶⁵ Although relatively safe in most patients, contrast agents may be quite harmful to others.

The American College of Radiology Manual on Contrast Media (2013)¹⁶⁶ indicates that patients with a history of prior allergy-like reaction to contrast media, history of asthma, renal insufficiency, significant cardiac disease, and elevated anxiety are at an increased risk of experiencing adverse IV contrast-material reactions.¹⁶⁶ Some reactions, in fact, may be life threatening. In 2006, some gadolinium-based contrast agents (GBCAs) were linked with nephrogenic systemic fibrosis (NSF), a scleroderma-like, fibrosing condition, that could be potentially fatal in patients with renal failure.¹⁶⁷

The American College of Radiology manual¹⁶⁶ estimates that “patients with end-stage chronic kidney disease (CKD) (CKD5, eGFR [estimated glomerular filtration rate] <15 ml/min/1.73 m²) and severe CKD (CKD4, eGFR 15 to 29 ml/min/1.73 m²) have a 1 percent to 7 percent chance of developing NSF after one or more exposures to at least some GBCAs.” In 2010, the U.S. Food and Drug Administration (FDA) issued a warning for use of GBCAs in patients with kidney dysfunction. Agents such as Magnevist, Omiscan, and Optimark, the agency states, place certain patients with kidney dysfunction at higher risk for NSF than other GBCAs.¹⁶⁸ FDA had previously issued a Public Health Advisory (2006) about the possible link between exposure to GBCAs for magnetic resonance angiography and NSF in patients with kidney failure.¹⁶⁹ The FDA later (2007) required a box warning on product labeling of all GBCAs used in MRIs regarding the risk of NSF in patients with severe kidney insufficiency, patients just before/just after liver transplantation, or individuals with chronic liver disease.¹⁷⁰

Six MRI-related studies enrolled at-risk patients;^{86,158,160,161,163,164} five studies evaluated GBCAs in patients at-risk for kidney or liver disease.^{86,158,160,161,163} The largest study (N=84,621) surveyed 19,354 (22.9%) patients at-risk with renal and liver dysfunctions, history of allergies, hypertension, chronic heart disease, and central nervous system disorders who received manual (74.5%) or automated (25.5%) injections of Gd-DOTA.¹⁵⁸ In the study, 421 adverse events (65 different) occurred in 285 (0.34%) patients. Eight serious adverse events (less than 0.01%) were reported; life-threatening events in 3 patients. Ishiguchi and Takahashi (2010)¹⁶¹ also evaluated the safety of Gd-DOTA and reported a less than 1 percent overall incidence of adverse events. The authors indicated that general condition, liver disorder, kidney disorder, complication, concomitant treatments, and Gd-DOTA dose were statistically significant risk factors for adverse reactions.

Ichikawa et al. (2010) reported mostly mild adverse events in 178 patients with suspected focal hepatic lesions¹⁶⁰ after undergoing MRI with a single injection of Gd-EOB-DTPA. Voth et al. (2011)⁸⁶ retrospectively reviewed 34 clinical studies that had enrolled 4,549 patients receiving Gd-BT-DO3A and 1,844 patients receiving comparator agents (e.g., Gd-DTPA, Gd-HP-DO3A, Gd-DTPA-BMEA, or Gd-DTPA-A-BMA). Results indicated similar overall adverse event rates for both groups (4.0%) although slightly more serious adverse events occurred in the Gd-BT-DO3A group (0.4% vs. 0.2%). Lastly, Hammerstingl et al. (2009)¹⁶³ reported no serious or severe adverse events after randomly assigning patients with known focal liver lesions or suspected liver lesions to gadobutrol (N=292) or gadopentetate-enhanced MRI (N=280).

Five studies, also evaluating GBCA-enhanced MRIs, reported no harms,¹⁵⁶ mild gastrointestinal harms,¹⁶² mild burns from an MR coil,⁸⁷ and two severe adverse drug reactions (ADRs).^{157,159} One integrated retrospective analysis of six clinical studies¹⁵⁹ (N=14,299)

indicated that the “occurrence of ADRs...following...gadobutrol is comparable with the published data of other Gd-based contrast agents.” Lastly, one study focusing on general harms from MRI¹⁶⁴ enrolled 365 patients at-risk for developing breast cancer and reported significant MRI discomfort was mainly due to noise of the machine (64.6%). See Appendix C for details on MRI-related adverse events in these studies.

PET/CT

Harms Studies Specific to Pancreatic Cancer

There were no pancreas-specific studies on harms of PET/CT.

Recent Harms Studies Not Specific to Pancreatic Cancer

PET/CT-related harms were reported in 3,359 patients in one study.⁸⁷ A retrospective review of 3,359 PET/CT scans (106,800 scans overall)⁸⁷ reported four severe adverse events including chest pain (2) and shortness of breath (2). See Appendix C for details on PET/CT-related adverse events in these studies.

KQ3a. How are patient factors related to the harms of different imaging techniques?

No included studies addressed this subquestion.

KQ3b. What are patient perspectives on the tolerance of different imaging techniques and the balance of benefits and harms of different imaging techniques?

Key Points

- In the context of screening high-risk individuals (HRIs) for pancreatic cancer, about 10 percent of patients stated that EUS is “very uncomfortable,” and 11 percent stated that MRI is “very uncomfortable.”
- No pertinent evidence exists on other screening tests, or any imaging tests for diagnosis/staging.

Detailed Synthesis

One study addressed this question.¹⁷¹ Authors in the Netherlands enrolled 69 patients at high risk of having (or developing) pancreatic adenocarcinoma in a screening program. In the study “high risk” was defined as anyone with a first-degree relative with pancreatic cancer or anyone with a gene mutation prone to pancreatic cancer. The screening examinations involved both EUS and MRI, and all patients enrolled had received both imaging tests (testing interval between tests was a maximum of 2 weeks).

Patients were asked a question about their comfort level during EUS and MRI with this wording: “How did you experience undergoing an MRI? Was this experience: not uncomfortable, slightly uncomfortable, very uncomfortable or extremely uncomfortable.” For EUS, 10 percent of patients found it very uncomfortable, and for MRI this percentage was 11 percent. For EUS, the stated reason for lack of comfort involved either inadequate sedation or oversedation, whereas for MRI the stated reason involved claustrophobia. The authors also reported “there was no statistically significant difference in the frequency that respondents were

dreading the procedure,” but they did not report the percentages of patients feeling dread beforehand.

Conclusions for KQ3

In the diagnosis and staging of pancreatic adenocarcinoma, different imaging tests are associated with different types of harms. MDCT and PET/CT use radiation and therefore can theoretically contribute to future development of malignancy, but the size of the risk is not possible to estimate specifically when used for diagnosis/staging of pancreatic adenocarcinoma. EUS-FNA risks are due to the physical invasiveness of the procedure and primarily involve pancreatitis, postprocedural pain, and puncture, perforation, or bleeding. Regarding patient tolerance, one study of screening found that about 10 percent of patients state that EUS-FNA and MRI are very uncomfortable.

Test Performance of Imaging Modalities for Screening Asymptomatic Adults at High-Risk

KQ4: Imaging Techniques for Screening Asymptomatic People

Key Points

- No accuracy estimates are possible for any single imaging modality because the six included screening studies provided accuracy data only for combinations of imaging tests.
- Two percent to 18 percent of HRIs screened received either a biopsy or surgery based on imaging findings on any imaging modality— MDCT, EUS-FNA, or MRI— amounting to a total of 43 of 665 HRIs (7%) from all six studies.
- Of 46 patients with a pathological specimen from either biopsy or surgery in the six screening studies, 17 total (1.1% to 9.0% of HRIs screened) had true-positive findings (i.e., pathology-confirmed precursor lesions or pancreatic adenocarcinoma); 19 total (0% to 9.8% of HRIs screened) had major false-positive findings (i.e., patient had surgical resection based on imaging and pathology that showed a benign lesion, e.g., branch duct intraductal papillary mucinous neoplasia [BD-IPMN] with low-grade dysplasia); seven total (0% to 9.2% of HRIs screened) had a minor false-positive finding (i.e., patient had a FNA biopsy based on imaging but pathology was normal, so no surgery was performed). An additional three patients (0% to 1.5% of HRIs screened) had false-negative findings (i.e., patient’s cancer was missed on image screening but found on later screening with pathology confirmation).

Detailed Synthesis

Six primary studies met inclusion criteria for this question, of which five were recent (published in 2009 or later). The group of studies was heterogeneous in the populations studied, imaging tests examined, the study design, and reporting of results, which limits generation of conclusions.

Differences in populations studied resulted from different definitions of high-risk. Most studies used a combination of personal and family history of pancreatic cancer and/or a familial

cancer syndrome (i.e., familial pancreatic cancer) and/or a hereditary predisposition to tumors (i.e., Peutz-Jeghers syndrome). One study¹⁷² screened only individuals with a known *p16* gene mutation, which is associated with various cancers and found most prominently in pancreatic cancer.

Studies varied in the choice of imaging studies and screening protocols. One study¹⁷² examined the use of MRI only for screening HRIs, whereas the others looked at a combination of MRI/magnetic resonance cholangiopancreatography (MRCP) with EUS-FNA, some with the addition of MDCT and also ERCP. Two studies^{173,174} looked at one-time-only initial screening of HRIs, whereas four studies had followup screening annually or more frequently for individuals from whom it was indicated. Followup times ranged from 5 to 50.4 months through the studies.

All six studies were prospective, and none were randomized controlled trials; however, there were other differences in study designs. One study¹⁷⁵ had a control arm of 149 non-HRIs. Two studies^{173,175} reported some level of blinding to test interpretation; radiologists blinded to results of other imaging reports and endoscopists blinded to imaging results, and in one study, pathologists were unaware of clinical or radiologic findings.¹⁷⁵ In two studies,^{175,176} only one endoscopist performed all EUS-FNA procedures, and in two studies,^{175,177} only one radiologist performed radiologic interpretations of interest in the study (MRI and MDCT). However in other studies it was unclear and there was no stated accounting for variability in performance of EUS-FNA or interpretation of radiologic and EUS images. Studies' reference standard was not confirmed surgical pathology for all cases because most were not treated. Reference standard was "followup," which in some cases was a pathologic specimen (biopsy or surgical) only for those who warranted such interventions clinically, but in most cases was a clinical visit or followup imaging. The clinical judgment for surgery was determined in most cases by a multidisciplinary team according to institution-specific standards, in some cases with parameters around appropriate indications. In one multi-site study,¹⁷³ standard of care for surveillance and treatment was determined by each individual site.

Most of these studies were not designed to assess accuracy of individual imaging modalities for screening of HRIs, but rather the accuracy of screening HRIs with a combination of imaging modalities as deemed clinically appropriate. Similarly, they were not designed to assess comparative accuracy of imaging modalities. Therefore, studies did not uniformly nor comprehensively report results for each imaging modality performed, which prevents conclusions about accuracy of any particular imaging tests or comparative accuracy.

Data tables in Appendix D present the findings from the screening studies. From three of the six screening studies that reported such data, 52 percent to 63 percent of HRIs had completely normal imaging studies (for any imaging modality—MDCT, EUS-FNA, MRI) throughout the study periods. An additional 18 percent to 45 percent of HRIs from the same three studies had some abnormal imaging findings, but not sufficient to warrant biopsy or surgery during the study periods. Some of these abnormal findings, such as changes suggestive of pancreatitis, although noteworthy, were not deemed precursor lesions to pancreatic adenocarcinoma for which biopsy or surgical intervention was necessary. So within the three studies, two studies stated that 97 percent and one study stated that 81 percent of HRIs screened had no concerning imaging findings (by any imaging modality) that resulted in additional intervention.

Fourteen individuals (2.1%) from all six studies (total N=665) were found to have in situ or frank adenocarcinoma. While these rates are still relatively low, they are significantly higher among the HRI population than among the general population with an annual incidence of 0.014 percent.¹ However the desirable approach to screening is to uncover precursor lesions

before they become adenocarcinoma. Among all HRIs enrolled from all 6 studies, a total of 46 individuals (7% of all enrolled HRIs from 6 studies, with individual studies ranging from 2% to 18% of HRIs screened) had abnormal findings on imaging findings (on any imaging modality) that resulted in either a biopsy or surgery.

Of the total of 46 HRIs with a pathological specimen from either biopsy or surgery from all 6 screening studies, 17 total had true-positive findings (i.e., pathology confirmed precursor lesions or pancreatic adenocarcinoma). The true-positive findings for individual studies ranged from 1.1 percent to 9.0 percent of HRIs screened. Canto et al. (2012)¹⁷³ acknowledged a more conservative approach and had a lower rate of true positives along with Al-Sukhni (2012).¹⁷⁷ However Al-Sukhni also had two cases of false negatives in which biopsy-confirmed cancer lesions and precursor lesions were found on subsequent imaging screenings (4th and 5th rounds) that were not seen on initial imaging. Although we categorized this as a “false-negative” with respect to the imaging modalities’ ability to detect a precursor lesion, it is arguable whether the biology of the tumor is such that the rapid cancer development in HRIs is the primary attributable factor. The Vasen et al. (2011) study reported one false negative study in a patient who was diagnosed with pancreatic adenocarcinoma when symptoms developed 4 months after the negative screening MRI.¹⁷² The Canto et al. (2012)¹⁷³ study did not report any false negatives, but the authors also focused on a one-time initial screening and had an average followup period of 28 months (range, 14–47.2 months), perhaps not allowing for additional cases of undetected pancreatic cancers to be detected. Higher rates of true positives were observed in the studies by Verna (2010),¹⁷⁴ Vasen (2011),¹⁷² and Canto (2006)¹⁷⁵ (4.9%, 9.0%, 5.1%, respectively); also, these studies had higher rates of major false positives (5.1% to 9.8%) (i.e., patients went to surgery for benign lesions that were not deemed precancerous lesions). The challenge remains that certain lesions such as the various grades of IPMN and PanIN 1–3 cannot be reliably distinguished by imaging modalities. Even with FNA biopsy, Langer et al. (2009)¹⁷⁶ also reported high rates of false positives. In that same study, there were 7 cases of “minor false positives” in which the HRI had an FNA biopsy based on imaging and pathology that was normal, but surgery was avoided.

Individual study observations suggest that CT alone as an imaging modality for screening HRI may be insufficient.^{173,175} In Canto et al. (2012),¹⁷³ the authors noted fewer pancreatic lesions were detected by MDCT than by MRI and EUS-FNA. Individual study observations also suggest that EUS-FNA alone may “overcall suspicious lesions,”¹⁷⁷ but in combination with additional imaging such as MRI, it may be useful to prevent unnecessary surgery.

Conclusions for KQ4

The six included studies were not designed to assess accuracy of individual imaging modalities for screening of HRIs, but rather the accuracy of screening HRIs with a *combination of imaging modalities* as deemed clinically appropriate. Similarly, they were not designed to assess *comparative* accuracy of imaging modalities. Studies did not uniformly or comprehensively report results for each imaging modality performed, which prevents conclusions about accuracy for any particular imaging test or comparative accuracy. However, we describe some observations from the studies on various imaging modalities below.

MDCT has been the most used imaging modality for screening. Its advantages are that it is widely available, noninvasive, well-tolerated, and less dependent on test operators and interpreters. In certain populations at high risk for pancreatic cancer (e.g., Peutz-Jeghers syndrome, *BRCA2* mutation) who are also at high risk of developing other cancers (ovarian

cancer, melanoma), there may be additional utility to screening with imaging modalities such as MDCT (and MRI) because of the possibility of detecting other cancers outside of the pancreas and outside of the range of EUS. In a few studies^{174,175,177} extrapancreatic neoplasms were detected among HRIs (located in ovaries, kidneys, lung). In some studies, MDCT missed lesions that were detected through EUS.¹⁷⁵

Some studies report that MRI/MRCP has similar abilities to detect precursor lesions.¹⁷⁶ Moreover, MRI/MRCP has the advantage of not exposing patients to radiation, which is important, given the repeated nature of some screening regimens proposed. As mentioned above, MRI also has the ability to detect extrapancreatic lesions.

Advantages of EUS-FNA appear to include detection of pancreatic masses smaller than 1 cm, and FNA also allows for tissue sampling to aid in diagnosis. Disadvantages to EUS-FNA include that it is less readily available, more operator dependent, and more invasive than other imaging modalities. Authors of one study believe that EUS-FNA “overcalled” or overdiagnosed suspicious lesions, leading to unnecessary surgical resection.¹⁷⁵ Studies reviewed have suggested the use of EUS-FNA as an adjunct to another screening modality such as CT or MRI.^{175,177} Taken as a whole, the studies examined provide no evidence for conclusions about which imaging modalities are best for screening asymptomatic HRIs for pancreatic cancer screening.

Discussion

Key Findings and Strength of Evidence

For single-test accuracy, we summarized results from relevant systematic reviews to estimate the accuracy of each imaging modality. With regards to diagnosis and judging resectability in patients with unstaged disease, we drew the following conclusions:

- For diagnosis using multidetector computed tomography (MDCT), one systematic review yielded a sensitivity estimate of 91 percent (95% confidence interval [CI], 86% to 94%) and a specificity estimate of 85 percent (95% CI, 76% to 91%). (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using endoscopic ultrasound with fine-needle aspiration (EUS-FNA), four high-quality and recent systematic reviews yielded sensitivity estimates ranging from 85 percent to 93 percent and specificity estimates ranging from 94 percent to 100 percent. (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using magnetic resonance imaging (MRI), three systematic reviews yielded sensitivity estimates of 84 percent to 86 percent and specificity estimates of 82 percent to 91 percent. (Strength of evidence from published systematic reviews was not graded.)
- For diagnosis using positron emission tomography–computed tomography (PET/CT), three systematic reviews yielded sensitivity estimates of 87 percent to 90 percent and specificity estimates of 80 percent to 85 percent. (Strength of evidence from published systematic reviews was not graded.)
- In assessing the resectability of the cancer in patients with unstaged disease using MDCT, one systematic review yielded a sensitivity estimate of 81 percent (95% CI, 76% to 85%) and a specificity estimate of 82 percent (95% CI, 77% to 97%). (Strength of evidence from published systematic reviews was not graded.)
- In assessing the resectability of cancer in patients with unstaged disease using MRI, one systematic review yielded a sensitivity estimate of 82 percent (95% CI, 69% to 91%) and a specificity estimate of 78 percent (95% CI, 63% to 87%). (Strength of evidence from published systematic reviews was not graded.)

Also for single-test accuracy, regarding staging and judging resectability in patients whose disease has been staged, we drew the following conclusions:

- Two systematic reviews that were not assessed as high quality reported on computed tomography (CT) for assessing vascular invasion. Both concluded that sensitivity and specificity were worse for the subset of studies using older or single-slice CT scanners than for the studies using newer multi-slice CT. Summary sensitivity values for the newer scanners ranged from 80 percent to 85 percent and summary specificity ranged from 82 percent to 97 percent. The evidence base in both reviews was small: four or five studies each. (Strength of evidence from published systematic reviews was not graded.)
- One systematic review that was not high quality reported on magnetic resonance (MR) for assessing vascular invasion, concluding it had sensitivity of 63 percent and

- specificity of 93 percent. The evidence base was only four studies. (Strength of evidence from published systematic reviews was not graded.)
- One review of PET/CT included only a single study, which had reported 82 percent sensitivity and 97 percent specificity for detecting liver metastasis. (Strength of evidence from published systematic reviews was not graded.)

For comparative accuracy, our conclusions appear in Table 15. For diagnosis, we found evidence to support the claim that MDCT and MRI are similarly accurate. We also concluded that MDCT and EUS-FNA are similarly accurate when determining whether an unstaged tumor can be resected. This is an important finding, because MDCT is the standard method of evaluating suspected pancreatic cancer and is often used to guide the key clinical decision of whether or not to operate. Using EUS-FNA instead of MDCT for this purpose would have no impact on the rates of appropriate resection, but it could alter other aspects such as procedural harms (fewer iatrogenic cancers, more iatrogenic pancreatitis and postprocedural pain). We note that surgical planning clearly requires more than just EUS-FNA, and so surgery would not be performed based on EUS-FNA alone.

Turning to staging, we found T (tumor) staging was better with EUS-FNA than MDCT. This may mean more accurate planning of neoadjuvant therapy if EUS-FNA is used. However, as above, this is less important since the key clinical issue is resectability. Two key factors in determining resectability are involvement of blood vessels and the presence of metastatic disease. Regarding the involvement of blood vessels we found that MDCT and MRI are similarly accurate. Regarding detection of metastatic disease we found that PET/CT has a slight advantage over MDCT (statistically significant advantage in specificity and a slight advantage in sensitivity). We note that both technologies had poor accuracy in detecting metastases (sensitivities of 57% for MDCT and 67% for PET/CT) but were quite good at ruling out metastases (specificities of 91% for MDCT and 100% for PET/CT).

Table 15. Summary of conclusions on comparative diagnostic and staging accuracy

Conclusion	# Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence
MDCT and MRI have similar accuracy in the diagnosis of pancreatic adenocarcinoma in symptomatic adults	7 (Total N=397)	Moderate	Direct	Consistent	Precise	No	Moderate
MDCT and EUS-FNA have similar accuracy in assessing resectability of pancreatic adenocarcinoma in symptomatic adults with unstaged disease	1 (Total N=53)	Low	Direct	Unknown	Precise	No	Low
EUS-FNA is more accurate than MDCT in assessing the T stage of pancreatic adenocarcinoma in symptomatic adults	1 (Total N=49)	Low	Direct	Unknown	Precise	No	Low
MDCT and MRI have similar accuracy in the assessment of the vessel involvement of pancreatic adenocarcinoma in symptomatic adults	3 (Total N=213)	Low	Direct	Consistent	Imprecise	No	Moderate
PET/CT is more accurate than MDCT in assessing metastases of pancreatic adenocarcinoma in symptomatic adults	2 (Total N=96)	Moderate	Direct	Consistent	Precise	No	Low

EUS-FNA = Endoscopic ultrasound with fine-needle aspiration; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; PET/CT = positron emission tomography-computed tomography; T = tumor.

The literature describes different procedural harms associated with each of the common modalities examined in the diagnosis and staging of pancreatic adenocarcinoma. MDCT and PET/CT both involve radiation and, therefore, can cause cancer. However, it is not possible to quantify the risk specific to the use of these tests for the diagnosis or staging of pancreatic adenocarcinoma. Pancreatitis, postprocedural pain, and puncture, perforation, and bleeding are all associated with EUS-FNA and stem from the physical invasiveness of this procedure. There is a paucity of data regarding patient tolerance. One study of screening found that about 10 percent of patients state that EUS-FNA and MRI are very uncomfortable.

The literature on screening studies did not provide comparative accuracy data for single-test or multiple-test strategies. Studies addressed different populations of high-risk individuals (HRIs). While screening imaging studies did identify some HRIs with pancreatic adenocarcinoma, there were also false positive and false negative results. A major barrier to effectively defining an optimal pancreatic cancer–screening approach is the evolving understanding of the unique biology of pancreatic cancers among HRIs, particularly those with strong genetic predispositions. However, rapid progression and cancer development occurred in some HRI individuals, showing that despite aggressive screening approaches, the natural history of some lesions in HRIs (i.e., familial pancreatic neoplasia) can be aggressive and are still not well understood. Defining and characterizing the appropriate high-risk populations for screening also needs to be further explored.

The development of optimal screening algorithms for HRIs is further complicated by evolution in the understanding of precursor lesions such as intraductal papillary mucinous neoplasia (IPMN) and pancreatic intraepithelial neoplasia (PanIN) lesions. Current imaging technologies are insufficient to differentiate between the low-grade and high-grade dysplasia in IPMNs and PanINs. One consensus-based guideline published in 2012 suggested that main duct IPMN should be resected, whereas branch duct IPMN without high-risk pathology and imaging features (i.e., high-grade dysplasia, increasing size) should be monitored. This reliance on both pathology and radiology to distinguish between high and low grade lesions creates a difficult situation in cases in which an IPMN or PanIN is suspected on imaging. Specifically, although surgical resection is the main treatment for precursor lesions, the timing of surgery versus continued imaging surveillance requires further study, particularly given the potential morbidity and mortality associated with pancreatic surgery.

Findings in Relationship to What is Already Known

We identified five reviews whose purpose was to compare different imaging modalities for the diagnosis and/or staging of pancreatic adenocarcinoma. One²⁸ required that all studies make direct comparisons (as we did in this report for KQ1b through 1g, and KQ2b through 2g), whereas the others did not set that requirement; instead, the reviewers performed an indirect comparison of studies of one modality to studies of another modality. The next five paragraphs discuss the four reviews, along with discussion of how they relate to our conclusions on comparative accuracy (see previous section). Then, we discuss a single identified systematic review of morbidity after EUS-FNA, and how it relates to our findings for KQ3.

Wu et al. (2012)⁴⁸ indirectly compared PET/CT with diffusion-weighted MRI, and included 16 studies. Authors concluded that PET/CT was highly sensitive and diffusion-weighted MRI was highly specific, and that “enhanced PET/CT seems to be superior to unenhanced PET/CT.” The data they analyzed, however, do not support any assertions of reliable differences among the modalities. The sensitivity of PET/CT was 87 percent, with a reported confidence interval from

81 percent to 82 percent, which must be a typographical error (we contacted the author for a correction, but received no reply). For diffusion-weighted MRI, the sensitivity was 85 percent with a confidence interval from 74 percent to 92 percent, so the sensitivity of MRI could actually have been higher than for PET/CT. Specificities for PET/CT and MRI were 83 percent and 91 percent, respectively, but imprecision means an important difference cannot be excluded by the data. The only comparative statement involves different forms of PET/CT, and we did not include any studies making such a comparison. The authors' conclusion was based on indirect comparisons, which we chose not to make in this review.

Tang et al. (2011)⁵⁰ indirectly compared PET/CT, PET alone, and EUS with or without FNA. Some of the EUS studies may have not permitted FNA (even if a lesion had been seen), thus those data are outdated. Authors included 51 studies published up to April 2009 and concluded that for diagnosis, PET/CT was the most sensitive of the three modalities (90%, vs. 88% for PET alone and 81% for EUS), whereas EUS was the most specific (93%, vs. 80% for PET/CT and 83% for PET alone). The authors concluded, based on these results, that PET/CT and EUS could play different clinical roles (e.g., PET/CT for ruling in disease, and EUS for ruling out disease). These authors did not compare technologies to MDCT, whereas all of our conclusions about comparative accuracy involved MDCT, so their conclusions neither conflict with nor confirm ours.

Dewitt et al. (2006)²⁸ directly compared CT (either single detector or multidetector) to EUS (either with or without the ability to perform FNA). Thus, some of the included studies used modalities that are outdated. Authors included 11 pre-2005 studies, each comparing the two technologies, and found there were several methodological flaws, such as retrospectivity and unrepresentative study populations. Despite these flaws, the authors concluded that EUS is more sensitive than CT for diagnosis; for staging and vascular invasion, no conclusion can be reached; and for resectability assessment, the data suggest equivalence. This review reached the same conclusion about resectability, but did not conclude that EUS is more sensitive (or more accurate in general) than MDCT. In comparing EUS-FNA to MDCT for diagnosis, we performed a meta-analysis of three studies. This evidence suggested a slight advantage of EUS-FNA, but the difference was not statistically significant and was too imprecise to permit a conclusion of similar accuracy. The difference may involve the inclusion of single-slice CT by Dewitt (which we excluded because it is an outdated technology).

Bipat et al. (2005)⁵³ indirectly compared "conventional" CT, helical CT, MRI, and transabdominal ultrasound for diagnosis and resectability of pancreatic cancer. The 68 included studies had been published between January 1990 and December 2003; thus, the imaging technologies assessed are outdated (e.g., single-detector CT). For diagnosis, helical CT dominated the other techniques (highest sensitivity and highest specificity). For determining resectability, the technologies had similar sensitivities (81% to 83%); however, helical CT had slightly better specificity at 82 percent as compared with 78 percent for MRI, 76 percent for conventional CT, and 63 percent for transabdominal ultrasound. In terms of correspondence to this review, we concluded similarity between MDCT and MRI, which is largely consistent.

Li et al. (2013)⁷⁶ compared CT, MR, and EUS without FNA for assessing vascular invasion in primary pancreatic adenocarcinoma. They analyzed four MR studies and twelve CT studies, with a subgroup of four of the latter studying MDCT. They concluded that CT was the most sensitive modality, while all three modalities had similar specificity. Most of the direct comparisons of CT and MR involved single-slice CT, so the authors' conclusions are based on indirect comparisons of CT to MR. The summary sensitivity for MDCT reported in the review

was 80 percent (95% CI, 70% to 89%) and the specificity was 97 percent (CI 93% to 100%). The summary sensitivity for MR was 63 percent (CI 48% to 77%) and the specificity was 93 percent (CI 86% to 98%). By contrast, this review found two studies directly comparing MDCT and MRI for assessing vascular invasion, and we found similar sensitivity (68% for MDCT and 62% for MRI) and specificity (97% for MDCT and 96% for MRI). The reason for the different sensitivity conclusion is unclear, but may be due to their use of an indirect comparison (i.e., perhaps the vessel involvement of patients in their four MDCT studies was easier to detect than the vessel involvement of patients in their four MRI studies).

Regarding procedural harms, one systematic review summarized data on EUS-FNA.¹⁷⁸ The authors included 51 articles, and among these studies a total of 8,246 patients had received the procedure for pancreatic indications. Using non-meta-analytic techniques (dividing the total number of incidents by the total number of patients in the studies), they estimated the rates of 0.44 percent for pancreatitis (36/8,246), 0.38 percent for postoperative pain (31/8,246), 0.08 percent for fever (7/8,246), 0.1 percent for bleeding (8/8,246), 0.02 percent for perforation (2/8,246), and 0.01 percent for infection (1/8,246). The authors also investigated whether the observed rates differed among prospective and retrospective studies. For pancreatitis, they found rates of 0.67 percent in prospective studies but only 0.37 percent in retrospective studies. For postoperative pain, they found rates of 1.4 percent in prospective studies but only 0.09 percent in retrospective studies. The authors did not report the statistical significance of these differences, so we performed the chi-square test and found that the difference for pancreatitis was not statistically significant ($X^2(1)=2.95$, $p=0.09$), but it was for postoperative pain ($X^2(1)=64.1$, $p<0.05$).

Our review found similarly low rates of procedural harms of EUS-FNA and that the most commonly reported harms are pancreatitis and postoperative pain. We did not attempt to estimate rates because of the wide variation in study methods and reporting. Because of the finding regarding prospective/retrospective studies, however, we investigated whether the finding was apparent in the studies we reviewed for KQ3. It was not. For pancreatitis, findings were in the opposite direction (0.39% for prospective studies, 0.46% for retrospective studies). For pain, findings were in the same direction, but the difference was smaller (1% in prospective studies, 0.7% in retrospective studies). The reason for the difference may involve our more-stringent inclusion criteria. We had required that included studies for harms stated in their Methods sections a plan to measure harms; this was intended to exclude studies that reported harms data only anecdotally. If such anecdotal reports are more common among retrospective studies (a reasonable supposition), then our criteria may explain the difference.

Implications for Clinical and Policy Decisionmaking

Pancreatic adenocarcinoma carries a poor prognosis, in part due to advanced-stage presentation and diagnosis. While the incidence of pancreatic cancer is relatively low, it appears to be rising, increasing by 1.5 percent per year, which is beyond the rate expected based on aging of the population. Some predictions suggest that pancreatic adenocarcinoma will be the second highest incident cancer by 2020. This evidence review compares and summarizes current evidence on the effectiveness of imaging modalities (MDCT, MRI, EUS-FNA, and PET/CT) commonly used for diagnosing, staging, and determining the resectability of pancreatic cancer. In this report, the evidence was usually too imprecise to permit conclusions, but we found sufficient evidence for some tentative evidence-based conclusions, outlined next.

For diagnosis, we found MDCT and MRI have similar accuracy for diagnosing pancreatic adenocarcinoma. Specifically, we estimated a positive predictive value (PPV) of 90 percent and a negative predictive value (NPV) of 88 percent for both of these imaging procedures. In other words, a patient with a positive test result (on either MDCT or MRI) has approximately a 90 percent chance of having pancreatic adenocarcinoma, whereas a patient with a negative test result (on either MDCT or MRI) has only a 12 percent chance of having pancreatic adenocarcinoma. Examination of studies comparing PET/CT versus MDCT or EUS-FNA did not allow us to draw conclusions regarding comparative accuracy for diagnosis, because of low-quality or limited evidence.

For staging, we found that EUS-FNA is more accurate than MDCT for T staging (tumor size). The comparative accuracy of EUS-FNA over other technologies for diagnosis and staging was mostly unclear, although for resectability we did find it was similar to MDCT (detailed below).

In the staging assessment of metastases (M staging), PET/CT was more accurate than MDCT. A positive MDCT result indicates an 80 percent chance of actually having metastases (i.e., PPV of 80%), whereas a positive PET/CT result indicates a near 100 percent chance (i.e., PPV of 100%). A negative MDCT scan indicates a 23 percent chance of having metastases (i.e., NPV 23%), whereas a negative PET/CT scan indicates a 17 percent chance of having metastases (i.e., NPV 17%). M staging was the only area in which PET/CT was found superior to other imaging modalities.

In assessing vessel involvement, MDCT and MRI had similar accuracy. We estimate that a positive test result (on either MDCT or MRI) indicates a 73 percent chance of vessel involvement (i.e., PPV of 73%), whereas a negative test result (on either test) indicates only a 5 percent chance (i.e., NPV of 5%).

For determining resectability of lesions in patients whose disease is not staged, MDCT and EUS-FNA were found to be similar in accuracy. Those whose cancer is deemed unresectable by either MDCT or EUS-FNA have about an 88 percent chance of it actually being unresectable (i.e., PPV of 88%), and those whose cancer is deemed resectable by either test have about a 70 percent chance of it actually being resectable (i.e., PPV of 70%). This is important because upfront determination by imaging or endoscopy that an individual's tumor is unresectable spares him/her surgery and its associated morbidity. It should be noted that using EUS-FNA instead of MDCT would have little impact on the rates of appropriate resection, but could alter other aspects such as procedural harms (fewer iatrogenic cancers, more iatrogenic pancreatitis and postprocedural pain).

MDCT angiography with 3D reconstruction is a newer technology, for which no conclusions could be drawn in this review because of limited evidence. One study that was performed by the software developers of the technology suggested a greater ability of MDCT angiography with 3D reconstruction to accurately detect resectability over MDCT that does not include reconstruction. Additional research would help verify and further elucidate the role of this imaging study in diagnosis and management of pancreatic cancer.

One of the practical challenges for this review is that although our key questions looked separately at the comparative effectiveness of imaging procedures for diagnosis, staging, and resectability, generally these determinations occur simultaneously or in rapid succession. So, the question naturally arises, do our findings mean that all four imaging modalities should be used in the evaluation of patients with suspected pancreatic adenocarcinoma? Specifically, should an individual have an MDCT or MRI for diagnosis, assessment of vessel involvement, and potential

resectability determination, followed by an EUS-FNA for tumor staging, followed by a PET/CT for metastatic staging? Although our results did not permit determination of the optimal sequencing of imaging tests, they do suggest that MDCT or MRI, plus EUS-FNA, plus PET/CT may all be appropriate for the diagnosis, staging, and resectability determination of suspected pancreatic adenocarcinoma.

The choice of which of these modalities an individual patient receives, however, is likely to be influenced by institutional availability, the risks of harms associated with each modality as well as patient preferences and tolerances. MDCT is the most widely available (12,700 scanners in 2012),¹⁷⁹ and although it is associated with the least amount of operator/interpreter dependence it does have the potential of harms from radiation exposure and administration of contrast dye. MRI (10,815 units in 2012)¹⁷⁹ and PET/CT (2,000 scanners in US in 2009)¹⁸⁰ are the next most available. These examinations are associated with slightly more operator/interpreter dependence; PET/CT exposes patients to radiation (predominantly through radioactive isotopes as opposed to CT technique), but MRI does not. Finally EUS-FNA is a highly specialized procedure that is currently less-widely available than the other modalities examined. Unlike the other imaging modalities, this procedure provides direct tissue sampling. However, it is associated with the most amount of operator dependence and also is associated with the most harms, including postprocedure pancreatitis, pain, gastrointestinal perforation, and bleeding. Patient perspectives identified in the literature were from studies screening high-risk populations for pancreatic cancer, in which both EUS-FNA and MRI were found in 10 percent and 11 percent of the population, respectively, to be “very uncomfortable.” However, given the poor prognosis of this disease, a “very uncomfortable” study that could provide significant information for diagnosis and management might be tolerable to an individual potentially facing such a grave diagnosis.

Existing practice follows a multi-modality paradigm that is largely institution-specific, based on technology and resource availability and institution and provider preference. This report sheds additional light on which imaging modalities are more accurate or roughly equivalent for some aspects of diagnosis and staging of pancreatic adenocarcinoma and could be incorporated into additional guidance developed for clinicians. Additional research, particularly among newer technologies such as MDCT angiography with 3D reconstruction or MRI angiography may be useful. However, it is uncertain if the improved resolution associated with newer imaging procedures will replace existing imaging or will simply add to the repertoire of preoperative evaluation.

Similarly, there is no uniform approach for pancreatic cancer screening among asymptomatic HRIs that is widely accepted. The U.S. Preventive Services Task Force recommends against screening for pancreatic cancer among the general population (i.e., average-risk persons), because of the low incidence of this disease. Consensus statements on approaches to a risk-based approach to screening exist¹⁸¹ but, again, are not supported by high-grade evidence. Some cost-effectiveness studies have even suggested that “doing nothing” or not screening is the most appropriate, cost-effective approach for HRIs at this time.¹⁸² Others have suggested that imaging and genetic and tumor marker evaluation should be restricted to the context of research.¹⁸³ Our goal was not to determine whether screening HRIs for pancreatic cancer was appropriate or effective, but rather to determine which imaging modalities might be more accurate for screening. Unsurprisingly, the literature on screening in HRIs includes multiple imaging procedures and in some cases includes genetic (i.e., *p16*, *BRCA2*) and/or tumor marker (i.e., CEA, CA19-9) testing in addition to imaging. Differences in the populations, differences in

choice of imaging modalities and protocols, differences in use of genetic and tumor markers and a limited number of studies creates significant difficulty in comparing various imaging modalities within a study and between studies. Thus, the studies examined provide no evidence for conclusions regarding comparative accuracy of imaging modalities for screening. At this time, further research is needed to elucidate the benefit of pancreatic screening among HRIs, including preferred imaging modalities and time intervals between imaging.

Reimbursement policies for these imaging modalities vary by payer. We examined the policies of a representative sample of payers to ascertain the status of MR, CT, PET/CT, and EUS-FNA. The most detailed policies were for PET/CT. While specific language varied, the plans we reviewed will reimburse for PET/CT only when CT and/or MR diagnosis and staging results are equivocal or inconclusive, or if those tests are contraindicated for a particular patient. Some policies had additional restrictions on use of PET/CT for restaging or follow-up of patients who have undergone treatment for pancreatic cancer. The policies we reviewed routinely covered CT, MRI, and EUS-FNA for diagnosis, staging, and restaging of pancreatic cancer.

Applicability

We judged the applicability of the evidence based on the PICO framework (patients, interventions, comparisons, and outcomes). Regarding patients, the typical age of patients in the included studies was 60–65 years. By contrast, in the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) database,⁵ the median age at diagnosis of pancreatic cancer from 2006 to 2010 was 71 years. The extent to which the accuracy of imaging tests varies by patient age is unclear. Resection may be more appropriate for younger patients (due to fewer comorbidities), but the comparative accuracy of different tests (e.g., MDCT vs. EUS-FNA) may not vary by age. In terms of gender, the typical percentage of patients who were female was 40 percent to 50 percent, and the SEER database reported annual incidence rates of 13.9/100,000 for men and 10.0/100,000 for women; these incidence rates suggest that approximately 42 percent of newly diagnosed cases of pancreatic cancer are in women. Thus, the gender ratio in the studies we included seems typical.

Regarding tests and comparisons, we included data only on imaging technologies that are currently in wide use for the diagnosis and staging of pancreatic adenocarcinoma. MDCT is widely used as the first imaging test for suspected pancreatic cancer, and most studies used CT. Specific test protocols, however, may differ between the studies we included and the typical test parameters used outside the context of a research study.

Regarding settings, most studies were conducted in university-based academic or teaching hospitals, which may limit the applicability of the results to community hospitals. Community hospitals may differ from the settings in the included studies with respect to the experience of the technicians administering the imaging test or the interpretation skills of those reading the imaging results. Bilimoria et al. (2007)¹⁸⁴ found that among 35,009 patients treated for pancreatic cancer, 54 percent were at community hospitals whereas only 38 percent were at academic hospitals (another 2% were at Veterans Administration hospitals). For the pancreas-specific studies we included, 77 percent were at academic hospitals. Thus, academic settings were overrepresented in the evidence we reviewed. The implication of this is unclear, but possibly the test readers or practitioners may be more experienced than at nonacademic centers.

Limitations of the Comparative Effectiveness Review Process

This section discusses problems that we encountered conducting this systematic review and how we addressed them. These problems included: (1) whether to include EUS-FNA as a technology of interest; (2) whether to address the issue of single-test accuracy; (3) how to assess the risk of bias of comparative accuracy studies; and (4) how to conceptualize study design and data abstraction for studies of screening.

A first challenge concerned EUS-FNA. Before our involvement, another Evidence-based Practice Center had recommended that this technology *not* be included in a comparative effectiveness review (CER) of “imaging tests” for pancreatic adenocarcinoma. The reason was that, unlike comparison technologies such as MDCT, EUS-FNA involves more than just imaging, because a biopsy can be performed. Thus, the concern was that any comparison would unfairly favor EUS-FNA. When we scanned the literature, it became clear that EUS-FNA for suspected pancreatic adenocarcinoma is very common and therefore was mentioned by numerous studies of diagnosis and staging. In order to maximize the relevance of our report, we decided to include it, and our Technical Expert Panel supported this decision.

A second challenge involved whether this CER should not only compare different imaging technologies but should also assess test performance data on each modality *in isolation* (i.e., noncomparative). Strictly interpreted, a “comparative” effectiveness review would only involve comparisons among modalities. However, we were aware of several systematic reviews providing some information about each test in isolation, and as long as the assessment was confined to these reviews, the focus would not be overly distracted from the main comparative questions. Thus, we decided to include two questions (KQ1a and KQ2a) on single test accuracy, limiting our resources to systematic reviews. These systematic reviews resulted in estimates for a subset of the information desired. However, several accuracy estimates have not been addressed by systematic reviews, and may potentially be addressed by *de novo* analyses of primary studies.

A third challenge involved assessing the risk of bias of *comparative accuracy* studies. The basic target for this assessment is whether a study comparing the accuracy of test A to that of test B (measuring both against a common gold standard) was biased in favor of one of the two tests. Ideally, we could have used an existing off-the-shelf assessment instrument. Current risk-of-bias instruments for diagnostic studies (e.g., QUADAS-2) do not sufficiently address this topic because they were designed for single-test accuracy studies (e.g., did this study provide unbiased estimates of test accuracy). We thought carefully about potential areas of bias and devised our own instrument for this purpose. The instrument has not been tested by others, and its appropriateness should be verified.

A fourth challenge concerned how to conceptualize study design and data abstraction for studies of screening. Screening for pancreatic precursor lesions is, by its very nature, a different clinical process from diagnosis and staging in symptomatic patients. The idea is not just to find pancreatic adenocarcinomas earlier, but to identify any precursor lesions, determine whether they should be resected, perform the necessary resections, and perform continued surveillance on those resected as well as those deemed lesion-free by initial screening. Thus, we faced challenges in categorizing the lesions found in the included screening studies and in synthesizing the data reported.

Limitations of the Evidence Base

Current evidence is limited in several ways, and below we discuss the two most important limitations: risk of bias and imprecision. Also, we mention reporting bias in the context of our searches of clinicaltrials.gov as well as our relevant quantitative analyses.

The first limitation concerns the risk of bias in the included studies. We judged most studies at moderate risk of bias, and this was due to several types of concerns:

- One concern is test timing: many studies did not report how many days, weeks, or months had elapsed between the two imaging tests. Given the relatively fast progression of pancreatic cancer, a long interval could cause an apparent difference in test accuracy even between two identically accurate tests.
- Another concern is an unbalanced availability of information: many studies did not report whether the readers of one test had the same information available as the readers of the other tests. Differential information could cause differential accuracy results.
- A third concern is the prior expertise of the readers: few studies reported that readers had similar levels of prior experience with the two tests under consideration. Greater experience with one test than the other could bias study results in favor of the first test. This could have resulted in a finding of a difference when in fact the tests are similarly accurate, or it could have resulted in a finding of no difference when in fact the second test is more accurate.

The other major limitation of the evidence is imprecision. In several instances regarding comparative test accuracy, the evidence was too imprecise to conclude that one test is better than another, or that the tests are similarly accurate. We performed meta-analyses to maximize the precision of the data, but still, we often judged the resulting summary statistics too imprecise to determine the direction of effect. For example, an ongoing question in the literature is whether MDCT and MRI are similarly effective in detecting metastases of pancreatic cancer. Our Technical Expert Panel had expressed the general belief that MRI can be better for detecting metastases to the liver. We performed a meta-analysis of five studies comparing the accuracy of these imaging technologies for detecting metastases. Both tests were generally poor, with a pooled sensitivity of about 50 percent (MDCT sensitivity was 48% with a 95% CI from 31% to 66%, as compared with MRI with a sensitivity of 50% and a 95% CI from 19% to 82%). The wide confidence intervals are due to the fact that these five studies had enrolled a total of only 54 patients with metastases from pancreatic cancer.

Regarding potential publication bias, we looked for evidence that earlier publications were more likely to report positive findings. We performed three quantitative analyses to investigate the correlation between the end recruitment dates and observed findings (in the 3 analyses containing 5 or more studies), but we did not find any reliable trends. We also searched clinicaltrials.gov, and did not identify any older trials that were unpublished. We identified eight relevant records (status as of March 2014):

- One (NCT00920023) was last updated in March 2013 and involved only a single imaging test (MRI); therefore, it would be included only for our KQ3 on harms. Few MRI studies report procedural harms, however, so this study is unlikely to have been included.
- Another (NCT00885248), with unknown recruiting status, will compare the accuracy of MDCT to PET/CT; it may be published in the future, but the entry has not been updated since 2009.

- A third (NCT00816179) was still recruiting and involves only EUS-FNA; such studies sometimes meet our inclusion criteria for harms, so it should be considered during updates.
- A fourth (NCT01717196) was ongoing but not recruiting and compares different aspirate volumes with EUS-FNA with respect to accuracy and complications. The complications data should be considered for updates.
- A fifth (NCT01662609) was still recruiting and has a purpose of determining “whether Endoscopic Ultrasound (EUS) can detect early stage pre-cancerous or cancerous changes in the pancreas in patients at high-risk for the development of pancreatic cancer.” The estimated study completion date is September 2017.
- A sixth (NCT00714701), denoted the CAPS4 study, was still recruiting at Johns Hopkins University. It includes five different high-risk groups and two controls, one of which is a group of patients with chronic pancreatitis. There may be overlap with patients in the CAPS studies included for KQ4.
- A seventh (NCT01997476) was ongoing but not recruiting and involves the diagnosis of chronic pancreatitis (a differential diagnosis) using three imaging modalities.
- An eighth (NCT00548626) was ongoing but not recruiting and involves the use of multiple needles compared with a single needle for EUS-FNA for the diagnosis of pancreatic neoplasms.

Research Gaps

For characterizing gaps, we used the Hopkins EPC framework proposed by Robinson et al. (2011).¹⁸⁵ That system suggests that reviewers identify a set of important gaps and determine the most important reason for each gap. Each gap should be assigned one of the following reasons for the inability to draw conclusions:

- A. Insufficient or imprecise information: no studies, limited number of studies, sample sizes too small, estimate of effect is imprecise
- B. Information at risk of bias: inappropriate study design; major methodological limitations in studies
- C. Inconsistency or unknown consistency: consistency unknown (only 1 study); inconsistent results across studies
- D. Not the right information: results not applicable to population of interest; inadequate duration of interventions/comparisons; inadequate duration of followup; optimal/most important outcomes not addressed; results not applicable to setting of interest

The first important gap concerns the general lack of specific evidence on MDCT angiography. This newer technology had been suggested by one of our Technical Experts as a key technology of interest in the context of the diagnosis and staging of pancreatic adenocarcinoma. Our review included only a single study of this technology; thus, the primary reason for the inability to draw conclusions is insufficient or imprecise information.

The second important gap concerns the lack of evidence on comparative longer-term outcomes such as how patients were managed differently after different tests, the length of survival after undergoing different imaging tests, and the quality of patients’ lives after different tests. No studies have provided comparative health outcome or quality of life information in the context of diagnosis and staging of pancreatic adenocarcinoma; thus, the reason for this gap is insufficient or imprecise information.

The third important gap concerns the lack of evidence on important factors that could influence comparative accuracy, such as the prior experience of test readers (e.g., 2 tests may have similar accuracy if readers are very experienced, but 1 may be much better if readers are less experienced), patient factors (e.g., for patients with jaundice, 1 test may be better, but for patients without jaundice that same test is worse), and tumor characteristics (e.g., for staging small tumors, 1 test is best, but for large tumors, another test is best). Again, no studies provided pertinent data, so the reason for this gap is insufficient or imprecise information.

The fourth important gap concerns the screening of asymptomatic high-risk people. No studies have reported test-specific screening accuracy (insufficient or imprecise information). This is an important gap in the literature because there is little evidence to justify the choice of one screening test over another.

Future research could address these gaps by conducting studies specifically designed to answer the important gaps. For example, to determine whether patients live longer after undergoing MDCT for diagnosis as compared with undergoing EUS-FNA for diagnosis, a future study could randomly assign patients suspected of having pancreatic adenocarcinoma to receive only one of the two modalities. Sufficient followup of all patients should be used to determine which group of patients lives longer. This would represent direct evidence on the most important outcome, survival.

Randomized trials may never be performed, but existing study designs (e.g., studies comparing the diagnosis performance of different modalities) could be analyzed more comprehensively to address other identified gaps. For example, symptoms vary greatly from patient to patient (degree of jaundice, weight loss, abdominal pain). One key gap involved the absence of information on whether comparative test accuracy was influenced by such patient factors. Addressing this gap would not require novel study designs, but simply involves additional analyses of data already being collected in the field.

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Abbreviations and Acronyms

95% CI:	95% confidence interval
AJCC:	American Joint Committee on Cancer
BD-IPMN:	branch duct intraductal papillary mucinous neoplasia
CER:	comparative effectiveness review
CINAHL:	Cumulative Index to Nursing and Allied Health Literature database
CKD:	chronic kidney disease
cm:	centimeter
CT:	computed tomography
EPC:	Evidence-based Practice Center
ERCP:	endoscopic retrograde cholangiopancreatography
EUS:	endoscopic ultrasound
EUS-FNA:	endoscopic ultrasound with fine-needle aspiration
FDA:	U.S. Food and Drug Administration
FDG:	¹⁸ F-fluorodeoxyglucose
GBCA:	gadolinium-based contrast agent
HRI:	high-risk individual
IPMN:	intraductal papillary mucinous neoplasia
IV:	intravenous
kg:	kilogram
KQ	Key Question
M stage:	metastases stage
MDCT:	multidetector computed tomography
MD-IPMN:	main duct intraductal papillary mucinous neoplasia
MHz:	megahertz
mg:	milligram
mL:	milliliter
mm:	millimeter
mm Hg:	millimeters of mercury
MRCP:	magnetic resonance cholangiopancreatography
MRI:	magnetic resonance imaging
N:	number
N stage:	nodal stage
NA:	not applicable
NR:	not reported
NS:	not significant
NSF:	nephrogenic systemic fibrosis
p:	probability value
PanIN:	pancreatic intraepithelial neoplasia
PET:	positron emission tomography
PET/CT:	positron emission tomography–computed tomography
QUADAS:	quality assessment tool for diagnostic accuracy studies
SD:	standard deviation
SEER:	Surveillance Epidemiology and End Results (National Cancer Institute)
SMA:	superior mesenteric artery
SMV:	superior mesenteric vein
T stage:	tumor stage
T:	Tesla

Glossary of Selected Terms

Blood vessel involvement—The extent to which the tumor surrounds or involves major blood vessels. The degree of surrounding (e.g., $<180^\circ$ or $>180^\circ$) and the specific blood vessel (e.g., superior mesenteric artery) will influence resectability. Venous involvement is generally more resectable than arterial involvement.

M staging—In the American Joint Committee on Cancer (AJCC) TNM system, M0 denotes a primary tumor that has not metastasized, and M1 denotes metastases. Metastatic cases are unresectable.

Metastases—Spread of the primary pancreatic tumor to other distant parts of the body (e.g., liver, peritoneum)

N staging—In the AJCC TNM system, N0 means regional lymph nodes are not involved, and N1 means they are. Lymph node involvement does not play a critical role in determining resectability.

Pancreatic adenocarcinoma—The most common type of pancreatic cancer; a solid tumor.

Pancreatitis—Inflammation of the pancreas.

Radiation—A harm of computed tomography that can increase the risk of developing cancer.

Resectability—The degree to which the tumor can be safely removed surgically. Resection is the only chance of cure for those who have pancreatic adenocarcinoma.

Sensitivity—The performance or likelihood of an imaging test to correctly detect cancer. It is computed by dividing the number of patients who test positive on the imaging test by the number of patients who were actually positive via the gold standard test.

Specificity—The performance or likelihood of an imaging test to correctly rule out cancer. It is computed by dividing the number of patients who test negative on the imaging test by the number of patients who were actually negative via the gold standard test.

T staging—In the AJCC TNM system, T staging indicates the primary tumor size and/or spread. T0 means there is no tumor; TX means unknown size/spread; Tis means carcinoma in situ; T1 means a tumor <2 cm and confined to the pancreas; T2 means a tumor >2 cm and confined to the pancreas; T3 means the tumor has extended outside the pancreas but not to nearby arteries; and T4 means the tumor has extended outside the pancreas to nearby arteries.¹⁰

Appendix A. Search Strategy

Table A-1. Search strategy

Set Number	Concept	Search Statement
1	Pancreatic Cancer/pancreas	exp pancreatic neoplasms/ or pancreas cancer/ or pancreatic cyst/
2		((exp pancreas/ or exp pancreas, exocrine/) and (neoplasm/ or adenocarcinoma/ or neoplasms/)) or pancreas tumor/ or Pancreatic neuroendocrine tumor/
3		(Pancrea\$ adj3 (mass\$ or cancer\$ or tumor?r\$ or sarcoma\$ or neoplasm\$ or carcinoma\$ or adenocarcinoma\$)).mp.
4		neuroendocrine tumors/ and pancrea\$.ti,ab.
5		Pancreatic neoplasms
6		4 not 5
7		1 or 2 or 3 or 6
8	Imaging	Endosonography/ or exp fluorodeoxyglucose F18/ or exp magnetic resonance imaging or exp positron-emission tomography/ or exp tomography, x-ray computed/ or exp ultrasonography/ or endoscopic echography/ or ultrasound/
9		Computer assisted emission tomography/ or computer assisted tomography/ or nuclear magnetic resonance imaging/ or positron emission tomography/
10		Exp Diagnostic imaging/ or exp magnetic resonance imaging/ or pancreas/ra or pancreas/us or pancreatic ducts/ra or pancreatic ducts/us
11		("computed tomography" or "positron emission" or "positron-emission" or "magnetic resonance" or "endoscopic ultraso\$" or "computer assisted emission tomography" or "computer assisted tomography" or computer-assisted tomography).ti,ab.
12		(SDCT or MDCT or FDG-PET or CT or PET or PET/CT or MRI or EUS).mp.
13		"Fludeoxyglucose positron emission tomography".mp.
14		((single?detector or multi?detector or multi?dimensional) adj (CT or "computed tomography")).mp.
15		(Endoscop\$ adj (ultrasound or ultrasonograph\$ or echograph\$)).ti,ab.
16		Or/8-15
17	Pancreatic cancer and imaging	7 and 16
18	Diagnosis	exp pancreatic neoplasms/di or pancreatic cyst/di
19		Diagnos\$.mp. or early diagnosis/ or diagnosis, differential/ or diagnosis/ or neuroendocrine tumor/di [Diagnosis]
20		pancreatic neoplasms/di, pa, us [Diagnosis, Pathology, Ultrasonography] or pancreas tumor/di [Diagnosis] or pancreas cancer/di
21		pancreatitis, chronic/di, pa, us [Diagnosis, Pathology, Ultrasonography] or chronic pancreatitis/di [Diagnosis]
22		17 and di.fs.
23		Or/18-22
24	Pancreatic cancer and imaging and diagnosis	17 and 23
25	Staging	Cancer staging/ or Neoplasm staging/
26		((mass\$ or cancer\$ or tumor?r\$ or sarcoma\$ or neoplasm\$ or carcinoma\$ or adenocarcinoma\$) and (biopsy or category or classification or classify or detect\$ or stage or diagnos\$ or staging)).ti,ab.
27		((mass\$ or cancer\$ or tumor?r\$ or sarcoma\$ or neoplasm\$ or carcinoma\$ or adenocarcinoma\$) and ("fine needle" or fine-needle or FNA or FNB or specimen or sample or sampling)).ti,ab.
28		Or/25-27

Set Number	Concept	Search Statement
29	Pancreatic cancer and imaging and staging	17 and 28
30	Diagnosis test – accuracy, specificity	17 and (exp diagnosis/ or di.fs.)
31		17 and (receiver operating characteristic/ or ROC curve/ or diagnostic accuracy/ or accuracy/)
32		17 and (precision or sensitivity or specificity or predict\$ or forecast\$ or likelihood or ((false or true) adj (positive or negative))).mp.
33		17 and (predictive value of tests/ or exp diagnostic errors/ or exp diagnostic error/)
34	Pancreatic cancer and imaging and diagnostic testing	Or/29-33
35	Screening	mass screening/ or early detection of cancer/ or population surveillance/
36		Cancer screening/ or cancer risk/ or risk factors/
37		(risk\$ or screen\$ or hereditary or inherit\$ or gene\$ or family history).ti,ab.
38		or/ 35-37
39	Pancreatic cancer and imaging and screening	17 and 38
40	Prognosis/survival	incidence/ or mortality/ or follow up studies/ or prognos\$.mp.or predict\$.mp. or course\$.mp. or (first and episode).ti,ab. Or cohort.ti,ab.
41		Exp “prediction and forecasting”/ or exp prognosis/ or exp survival rate/ or surviv\$.mp.
42		40 or 41
43	Pancreatic cancer and imaging and prognosis/survival	17 and 42
44	Combine sets to review	24 or 29 or 34 or 39 or 43
45	Limit by date	Limit 44 to yr=“1990-2013”
46	Limit	Limit 45 to humans
47	Limit	Limit 46 to English language
48	Remove duplicates	Remove duplicates from 47

Appendix B. Full-Length Review of Excluded Studies

- Adamek HE, Albert J, Breer H, et al. Pancreatic cancer detection with magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography: a prospective controlled study. *Lancet*. 2000 Jul 15;356(9225):190-3. *No statement in the methods about plan to capture harms*
- Afify AM, al-Khafaji BM, Kim B, et al. Endoscopic ultrasound-guided fine needle aspiration of the pancreas. Diagnostic utility and accuracy. *Acta Cytol*. 2003 May-Jun;47(3):341-8. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*
- Agarwal B, Krishna NB, Labundy JL, et al. EUS and/or EUS-guided FNA in patients with CT and/or magnetic resonance imaging findings of enlarged pancreatic head or dilated pancreatic duct with or without a dilated common bile duct. *Gastrointest Endosc*. 2008 Aug;68(2):237-42; quiz 334. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*
- Ahmed SI, Bochkarev V, Oleynikov D, et al. Patients with pancreatic adenocarcinoma benefit from staging laparoscopy. *J Laparoendosc Adv Surg Tech A*. 2006 Oct;16(5):458-463. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*
- Ahn SS, Kim M-J, Choi J-Y, et al. Indicative findings of pancreatic cancer in prediagnostic CT. *Eur Radiol*. 2009;19(10):2448-2455. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*
- Ainsworth AP, Hansen T, Frstrup CW, et al. Indications for and clinical impact of repeat endoscopic ultrasound. *Scand J Gastroenterol*. 2010 Apr;45(4):477-82. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*
- Aithal GP, Anagnostopoulos GK, Tam W, et al. EUS-guided tissue sampling: comparison of “dual sampling” (Trucut biopsy plus FNA) with “sequential sampling” (Trucut biopsy and then FNA as required). *Endoscopy*. 2007 Aug;39(8):725-30. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*
- Alle V, Gurusamy KS, Kali A, et al. Role of Positron Emission Tomography (PET) in pancreatic resection for suspected pancreatic and periampullary cancer. *Int J Surg*. 2011;9(5):366. *Just a meeting abstract*
- Almadi MA, Aljebreen A, Azzam N, Eltayeb MO, Javed M, Alharbi O. Clinical predictors of resectability of pancreatic adenocarcinoma. *Gastroenterology*. 2013 May;144(5 Suppl 1):S662-3. *Just a meeting abstract*
- Al-Nahhas A, Win Z, Szyszko T, et al. What can gallium-68 PET add to receptor and molecular imaging? *Eur J Nucl Med Mol Imaging*. 2007 Dec;34(12):1897-1901. *Narrative review*
- Alsibai KD, Denis B, Bottlaender J, et al. Impact of cytopathologist expert on diagnosis and treatment of pancreatic lesions in current clinical practice. A series of 106 endoscopic ultrasound-guided fine needle aspirations. *Cytopathology*. 2006 Feb;17(1):18-26. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*
- Alsohaibani F, Girgis S, Sandha GS. Does onsite cytotechnology evaluation improve the accuracy of endoscopic ultrasound-guided fine-needle aspiration biopsy? *Can J Gastroenterol*. 2009 Jan;23(1):26-30. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*
- Amin Z, Theis B, Russell RC, et al. Diagnosing pancreatic cancer: the role of percutaneous biopsy and CT. *Clin Radiol*. 2006 Dec;61(12):996-1002. *Unclear whether biopsies were ultrasound-guided*
- Anand N, Tran AH, Karabalin N, Wu BU. The utility of endoscopic ultrasound (EUS) in preoperative staging of potentially resectable pancreatic cancer. *Gastroenterology*. 2013 May;144(5 Suppl 1):S208-9. *Just a meeting abstract*
- Anderson MA. Diagnostic and therapeutic applications of EUS in pancreatic disease. *Gastroenterol Hepatol*. 2007 Oct;3(10):768-771. *Narrative review*
- Anderson SW, Soto JA. Pancreatic duct evaluation: Accuracy of portal venous phase 64 MDCT. *Abdom Imaging*. 2009 Jan;34(1):55-63. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Andrawes SA, Hindy P, Taur Y, et al. Accuracy of endoscopic elastography for detection of malignant pancreatic mass lesions. Systematic review and meta-analysis. *Gastrointest Endosc.* 2012 Apr;75(4 Suppl 1):AB207. *No data specific to an imaging test of interest*

Ang TL, Teo EK, Ang D, et al. A pilot study of contrast harmonic endosonography using DEFINITY in the evaluation of suspected pancreatic and peri-ampullary malignancies. *J Interv Gastroenterol.* 2011 Oct;1(4):160-165. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Arabul M, Karakus F, Alper E, et al. Comparison of multidetector CT and endoscopic ultrasonography in malignant pancreatic mass lesions. *Hepatogastroenterology.* 2012 Jul-Aug;59(117):1599-603. *No data specific to an imaging test of interest*

Arcidiacono PG, Carrara S. Endoscopic ultrasonography: Impact in diagnosis, staging and management of pancreatic tumors. An overview. *JOP.* 2004 Jul;5(4):247-252. *Narrative review*

Ardengh JC, De Paulo GA, Ferrari Jr AP. Pancreatic carcinomas smaller than 3.0 cm: Endosonography (EUS) in diagnosis, staging and prediction of resectability. *HPB.* 2003;5(4):226-230. *No comparative specificity data*

Ardengh JC, Lopes CV, Campos AD, et al. Endoscopic ultrasound and fine needle aspiration in chronic pancreatitis: differential diagnosis between pseudotumoral masses and pancreatic cancer. *JOP.* 2007;8(4):413-21. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Ardengh JC, Lopes CV, de Lima LF, et al. Diagnosis of pancreatic tumors by endoscopic ultrasound-guided fine-needle aspiration. *World J Gastroenterol.* 2007 Jun 14;13(22):3112-6. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Ardengh JC, Lopes CV, De Lima LFP, et al. Cell block technique and cytological smears for the differential diagnosis of pancreatic neoplasms after endosonography-guided fine-needle aspiration. *Acta Gastroenterol Latinoam.* 2008 Dec;38(4):246-251. *Non-English*

Ardengh JC, Malheiros CA, Pereira V, et al. Endoscopic ultrasound-guided fine-needle aspiration using helical computerized tomography for TN staging and vascular injury in operable pancreatic carcinoma. *JOP.* 2009;10(3):310-7. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Arslan A, Buanes T, Geitung JT. Pancreatic carcinoma: MR, MR angiography and dynamic helical CT in the evaluation of vascular invasion. *Eur J Radiol.* 2001;38(2):151-159. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Arvold ND, Niemierko A, Mamon HJ, et al. Pancreatic cancer tumor size on CT scan versus pathologic specimen: implications for radiation treatment planning. *Int J Radiat Oncol Biol Phys.* 2011 Aug 1;80(5):1383-90. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Arya M, Mathur S, Sonpal N, et al. Maintaining yield while minimizing eus guided fna passes in a community hospital setting. *Am J Gastroenterol.* 2010;105:S411. *Just a meeting abstract*

Asagi A, Ohta K, Nasu J, et al. Utility of contrast-enhanced FDG-PET/CT in the clinical management of pancreatic cancer: impact on diagnosis, staging, evaluation of treatment response, and detection of recurrence. *Pancreas.* 2013 Jan;42(1):11-9. *No comparative specificity data*

Ashida R, Ioka T, Ishida N, et al. For early detection of pancreatic cancer. *J Gastroenterol Hepatol.* 2012 Dec;27:370. *Just a meeting abstract*

Aslanian H, Salem R, Lee J, et al. EUS diagnosis of vascular invasion in pancreatic cancer: surgical and histologic correlates. *Am J Gastroenterol.* 2005 Jun;100(6):1381-5. *No data specific to an imaging test of interest*

Azabdaftari G, Goldberg SN, Wang HH. Efficacy of on-site specimen adequacy evaluation of image-guided fine and core needle biopsies. *Acta Cytol.* 2010 Mar-Apr;54(2):132-137. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Aziz AM, Said T, Poovathumkadavil A, et al. Using Multidetector CT in Predicting Resectability of Pancreatic Head Tumors: Surgical and Pathologic Correlation. *J Egypt Natl Canc Inst.* 2010 Dec;22(4):233-9. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Baghbanian M, Salmanroghani H, Baghbanian A, Bakhtpour M, Shabazkhani B. Efficacy of multi-detector computerized tomography scan, endoscopic ultrasound, and laparoscopy for predicting tumor resectability in pancreatic adenocarcinoma. *Indian J Gastroenterol.* 2013 Nov;32(6):376-80. *Assumed no false positives, thus did not truly measure both sensitivity and specificity*

Baghbanian M, Shabazkhani B, Ghofrani H, et al. Efficacy of endoscopic ultrasound guided fine needle aspiration in patients with solid pancreatic neoplasms. *Saudi J Gastroenterol.* 2012 Nov-Dec;18(6):358-63. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Balthazar EJ. CT contrast enhancement of the pancreas: Patterns of enhancement, pitfalls and clinical implications. *Pancreatol.* 2012 Feb;11(6):585-7. *Narrative review*

Bang JY, Hebert-Magee S, Trevino J, et al. Randomized trial comparing the 22-gauge aspiration and 22-gauge biopsy needles for EUS-guided sampling of solid pancreatic mass lesions. *Gastrointest Endosc.* 2012 Aug;76(2):321-7. *N <50*

Bang JY, Trevino J, Ramesh J, et al. Randomized trial comparing the fanning and standard techniques for EUS-guided FNA of solid pancreatic mass lesions. *Gastrointest Endosc.* 2012 Apr;75(4 Suppl 1):AB445-AB446. *Just a meeting abstract*

Bao PQ, Johnson JC, Lindsey EH, et al. Endoscopic ultrasound and computed tomography predictors of pancreatic cancer resectability. *J Gastrointest Surg* 2008 Jan; 12(1): 10-6, discussion 16. *Correlated vessel involvement via imaging to actual resectability, thus not direct*

Barber TW, Kalff V, Cherk MH, et al. 18 F-FDG PET/CT influences management in patients with known or suspected pancreatic cancer. *Intern Med J.* 2011 Nov;41(11):776-83. *No data specific to an imaging test of interest*

Barreiro CJ, Lillemoe KD, Koniaris LG, et al. Diagnostic laparoscopy for periampullary and pancreatic cancer: what is the true benefit? *J Gastrointest Surg.* 2002 Jan-Feb;6(1):75-81. *No data specific to an imaging test of interest*

Bartsch DK. Familial pancreatic cancer. *Br J Surg.* 2003 Apr 1;90(4):386-387. *Narrative review*

Basir Z, Pello N, Dayer AM, et al. Accuracy of cytologic interpretation of pancreatic neoplasms by fine needle aspiration and pancreatic duct brushings. *Acta Cytol.* 2003 Sep-Oct;47(5):733-8. *Only a single imaging test of interest, and N <50*

Basnayake C, Moore G, Croagh D, et al. Analysis of factors that influence accuracy of endoscopic ultrasound-guided fine needle aspiration for solid pancreatic masses. *J Gastroenterol Hepatol.* 2012 Oct;27:51. *Just a meeting abstract*

Bhutani MS. Endoscopic ultrasonography. *Endoscopy.* 2007 Nov;39(11):1005-1009. *Narrative review*

Bipat S, Saffire SKS, Van Delden OM, et al. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: A meta-analysis. *J Comput Assist Tomogr.* 2005 Jul-Aug;29(4):438-445. *Duplicate*

Birchard KR, Semelka RC, Hyslop WB, et al. Suspected pancreatic cancer: Evaluation by dynamic gadolinium-enhanced 3D gradient-echo MRI. *AJR Am J Roentgenol.* 2005;185(3):700-703. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Bluen BE, Lachter J, Khamaysi I, et al. Accuracy and quality assessment of EUS-FNA: A single-center large cohort of biopsies. *Diagn Ther Endosc.* 2012;139563. Epub 2012 Oct 31. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Bolog N, Constantinescu G, Oancea I, et al. Magnetic resonance imaging of bile and pancreatic ducts: a retrospective study. *Rom J Gastroenterol.* 2004 Jun;13(2):91-7. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Boraschi P, Donati F, Gigoni R, et al. Mangafodipir trisodium-enhanced MR imaging of pancreatic disease. *Eur Radiol.* 2006 May;16(5):988-997. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Boraschi P, Donati F, Giloni R, et al. Secretin-stimulated multi-detector CT versus mangafodipir trisodium-enhanced MR imaging plus MRCP in characterization of non-metastatic solid pancreatic lesions. *Dig Liver Dis*. 2009 Nov;41(11):829-37. *No data specific to an imaging test of interest*

Borbath I, Van Beers BE, Lonnew M, et al. Preoperative assessment of pancreatic tumors using magnetic resonance imaging, endoscopic ultrasonography, positron emission tomography and laparoscopy. *Pancreatol*. 2005;5(6):553-61. *EUS accuracy directly influenced reference standard*

Brais RJ, Davies SE, O'Donovan M, et al. Direct histological processing of EUS biopsies enables rapid molecular biomarker analysis for interventional pancreatic cancer trials. *Pancreatol*. 2012 Jan-Feb;12(1):8-15. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Brandwein SL, Farrell JJ, Centeno BA, et al. Detection and tumor staging of malignancy in cystic, intraductal, and solid tumors of the pancreas by EUS. *Gastrointest Endosc*. 2001 Jun;53(7):722-7. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Breitkopf CR, Sinicrope PS, Rabe KG, et al. Factors influencing receptivity to future screening options for pancreatic cancer in those with and without pancreatic cancer family history. *Hered Cancer Clin Pract*. 2012 Jun 27;10(1). *Hypothetical imaging test*

Brimiene V, Brimas G, Strupas K. Differential diagnosis between chronic pancreatitis and pancreatic cancer: a prospective study of 156 patients. *Medicina (Kaunas)*. 2011;47(3):154-62. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Brix G, Nissen-Meyer S, Lechel U, et al. Radiation exposures of cancer patients from medical X-rays: How relevant are they for individual patients and population exposure? *Eur J Radiol*. 2009 Nov;72(2):342-347. *Only a single imaging test of interest, and did not meet criteria for harms/screening/patient perspectives*

Brugel M, Rummeny EJ, Dobritz M. Vascular invasion in pancreatic cancer: Value of multislice helical CT. *Abdom Imaging*. 2004 May-Apr;29(2):239-245. *Just a meeting abstract*

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Appendix C. Evidence Tables

Systematic Reviews

Table C-1. Key Question 1a systematic reviews: study characteristics

Study	Databases Searched	Search Start	Search End	Modalities	Inclusion Criteria	Exclusion Criteria	N articles Included	N Patients	Conclusions on Quality	Analysis Methods
Affolter et al. 2013 ¹	MEDLINE, EMBASE, Scopus	Not reported	Apr-12	EUS-FNA	Compared effect of needle sizes on any outcome, including complications or cost.	None reported	7	1,452	Reporting is inconsistent	Pooled sensitivity and specificity, needle passes, ease of puncture, risk of inadequate sample using Stata
Chen et al. 2013 ²	Pubmed, EMBASE, Web of Science	No limit	Oct-11	EUS-FNA	Sufficient data for 2 x 2, pathologic confirmation	None reported	31	4,840	Results did not significantly differ between high- and low-quality studies	Pooled sensitivity, specificity, and DOR; summary ROC using Stata, MetaDiSc, and SPSS

Table C-1. Key Question 1a systematic reviews: study characteristics, (continued)

Study	Databases Searched	Search Start	Search End	Modalities	Inclusion Criteria	Exclusion Criteria	N articles Included	N Patients	Conclusions on Quality	Analysis Methods
Hébert-Magee et al. 2013 ³	MEDLINE, Scopus	Jan-94	Mar-11	EUS-FNA	Published in English, sufficient data for 2 x 2, pathologic confirmation or clinical and imaging follow-up, diagnosis of ductal carcinoma	Data from non-ductal carcinoma	34	3,644	Moderate to good quality, no risk of spectrum bias	Pooled sensitivity, specificity, and DOR; summary ROC using RevMan and Stata
Madhoun et al. 2013 ⁴	MEDLINE, PubMed, other unnamed databases	Jan-94	Oct-11	EUS-FNA	<u>Compared two needle gauges</u> , pathologic confirmation and/or 6 month clinical follow-up, sufficient data for 2x2	None reported	8	1,292	Good, but risk of review bias	Pooled sensitivity and specificity, bivariate SROC using SAS
Wang et al. 2013 ⁵	Pubmed, EMBASE, Cochrane	No limit	Dec-12	Standalone PET, PET/CT	Intravenous FDG, sufficient data for 2 x 2, pathologic confirmation and/or 6 month clinical follow-up, N ≥ 10	Non-primary cancer, pre-operative radiotherapy or chemotherapy	PET/CT: 4, total: 39	159	None	Pooled sensitivity and specificity using Stata
Puli et al. 2013 ⁶	MEDLINE, EMBASE, CINAHL, Cochrane Central Reg., DARE, others	Jan-66	Jan-12	EUS-FNA	Published in English, pathologic confirmation and/or clinical follow-up, sufficient data for 2x2	None reported	41	4,766	Good: all studies met 4 to 5 of the 14 QUADAS criteria	Pooled sensitivity, specificity, and DOR; summary ROC

Table C-1. Key Question 1a systematic reviews: study characteristics, (continued)

Study	Databases Searched	Search Start	Search End	Modalities	Inclusion Criteria	Exclusion Criteria	N articles Included	N Patients	Conclusions on Quality	Analysis Methods
Chen et al. 2012 ⁷	MEDLINE, PubMed	Jan-02	Jan-12	EUS-FNA	Published in English, pathologic confirmation and/or 6 month clinical follow-up, sufficient data for 2x2	Cystic lesions and other specific types of malignancies	15	1,717	Results of high-quality studies were more consistent	Pooled sensitivity, specificity, and DOR; summary ROC using Meta-Disc
Hewitt et al. 2012 ⁸	MEDLINE	1997	2009	EUS-FNA	Published in English, pathologic confirmation and/or 6 month clinical follow-up, sufficient data for 2x2, N >10	STARD <13, included ampullary lesions	33	4,984	Results of high-quality studies were more consistent	Pooled sensitivity, specificity, and DOR; summary ROC using Meta-Disc
Wu et al. 2012 ⁹	MEDLINE, EMBASE, Cochrane Library, Scopus, others	Jan-95	Aug-11	MR (diffusion-weighted), PET/CT	Published in English, pathologic confirmation, sufficient data for 2x2, N >10, QUADAS >9/14	None reported	MR: 7, PET/CT: 9, total: 16	MR: 390, PET/CT: 414	Selected only high-quality articles	Hierarchical SROC using Stata
Wu et al. 2012 ¹⁰	MEDLINE, EMBASE, CANCELIT, Cochrane	Jan-01	Aug-11	MR (diffusion-weighted)	Published in English, pathologic confirmation and/or 6 month clinical follow-up, sufficient data for 2x2, N >10, QUADAS >9/14	None reported	11	586	Reference diagnosis frequently included MR results	Pooled sensitivity, specificity, and DOR; summary ROC using Meta-Disc and Stata

Table C-1. Key Question 1a systematic reviews: study characteristics, (continued)

Study	Databases Searched	Search Start	Search End	Modalities	Inclusion Criteria	Exclusion Criteria	N articles Included	N Patients	Conclusions on Quality	Analysis Methods
Tang et al. 2009 ¹¹	MEDLINE, EMBASE, Scopus, others	Jan-66	Apr-09	PET/CT, EUS (not FNA), PET	Published in English or Chinese, pathologic confirmation and/or 6 month clinical follow-up, sufficient data for 2x2, N >10, QUADAS >9/14	Cystic or neuroendocrine tumors, could not isolate data for individual modalities , co-existing disease	PET/CT: 7, EUS: 21, standalone PET: 27, total: 51	Not reported	Good (since QUADAS was used as inclusion criterion)	Pooled sensitivity, specificity, and DOR; summary ROC using Meta-Disc
Hartwig et al. 2008 ¹²	PubMed	Jan-66	Jul-08	EUS-FNA	No language restriction, N ≥40	None reported	EUS-FNA: 28, total 53	4,225	None	Median across studies
Bipat et al. 2005 ¹³	MEDLINE, EMBASE, CANCERLIT, Cochrane	Jan-90	Dec-03	CT, MR, ultrasound	Published in English or German, some reference test, sufficient data for 2x2, N ≥20	None reported	MR: 14, CT: 27, total: 68	MR: 1,099; CT: 2,782	None	Bivariate sensitivity, specificity and covariate analysis using SAS

Table C-2. Key question 1a systematic reviews: published results

Study	Modality	Method	Patient Subgroup	Diagnostic Decision	N Studies	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy	Significant Heterog.	Comment
Bipat et al. 2005 ¹³	CT	All	All	Initial diagnosis	23	91% (86%-94%)	85% (76%-91%)		Not reported	
Affolter et al. 2013 ¹	EUS-FNA	19 gauge	All	Initial diagnosis	3	See comment	See comment		Not reported	Data could not be abstracted.
Affolter et al. 2013 ¹	EUS-FNA	22 gauge	All	Initial diagnosis	7	78% (74%-81%)	100% (98%-100%)		Yes	
Affolter et al. 2013 ¹	EUS-FNA	25 gauge	All	Initial diagnosis	7	91% (87%-94%)	100% (97%-100%)		Yes	
Chen et al. 2013 ²	EUS-FNA	All	All	Initial diagnosis	31	89% (88%-90%)	96% (95%-97%)		Yes	
Hébert-Magee et al. 2013 ³	EUS-FNA	All	All	Initial diagnosis	34	88.6% (87.2%-89.9%)	99.3% (98.7%-99.7%)		Yes	
Madhoun et al. 2013 ⁴	EUS-FNA	22-gauge	All	Initial diagnosis	8	85% (82%-88%)	100% (98%-100%)		No	
Madhoun et al. 2013 ⁴	EUS-FNA	25-gauge	All	Initial diagnosis	8	93% (91%-96%)	97% (93%-99%)		No	
Puli et al. 2013 ⁶	EUS-FNA	All	All	Initial diagnosis	41	87% (86%-88%)	96% (95%-99%)		No	
Chen et al. 2012 ⁷	EUS-FNA	All	All	Initial diagnosis	15	92% (91%-93%)	95% (93%-98%)		Yes	Heterogeneity driven by a single outlier with lower sensitivity and specificity than other studies
Hewitt et al. 2012 ⁸	EUS-FNA	All	All (Note 1)	Initial diagnosis	33	85% (84%-86%)	98% (97%-99%)		Yes	
Hewitt et al. 2012 ⁸	EUS-FNA	All	All (Note 2)	Initial diagnosis	32	91% (90%-92%)	94% (93%-96%)		Yes	
Hartwig et al. 2008 ¹²	EUS-FNA	All	All	Initial diagnosis	28	median 83%	median 100%	median 88%	Not reported	
Wu et al. 2012 ⁹	MR	Diffusion-weighted	All	Initial diagnosis	7	85% (74%-92%)	91% (71%-98%)		Yes	All studies also included in previous review

Table C-2. Key question 1a systematic reviews: published results (continued)

Study	Modality	Method	Patient Subgroup	Diagnostic Decision	N Studies	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy	Significant Heterog.	Comment
Wu et al. 2012 ¹⁰	MR	Diffusion-weighted	All	Initial diagnosis	11	86% (79%-91%)	91% (81%-96%)		Yes	
Bipat et al. 2005 ¹³	MR	All	All	Initial diagnosis	11	84% (78%-89%)	82% (67%-92%)		Not reported	
Wang et al. 2013 ⁵	PET/CT	All	All	Initial diagnosis	4	90% (79%-95%)	85% (38%-98%)		Not reported	
Wu et al. 2012 ⁹	PET/CT	All	All	Initial diagnosis	9	87% (see comment)	83% (71%-91%)		Yes	Typographical error in published confidence interval
Tang et al. 2009 ¹¹	PET/CT	All	All	Initial diagnosis	7	90.1% (85.5%-93.6%)	80.1% (73.1%-86.0%)		Yes	Subgroup of retrospective studies also reported
Bipat et al. 2005 ¹³	CT	All	All	Resectability	32	81% (76%-85%)	82% (77%-97%)		Not reported	
Bipat et al. 2005 ¹³	MR	All	All	Resectability	7	82% (69%-91%)	78% (63%-87%)		Not reported	

Notes: 1– only malignant cytology defined as positive, 2– malignant, suspicious, or atypical cytology defined as positive

Table C-3. Key Question 2a systematic reviews: study characteristics

Study	Databases Searched	Search Start	Search End	Modalities	Inclusion Criteria	Exclusion Criteria	N Articles Included	N Patients	Conclusions on Quality	Analysis Methods
Li et al. 2013 ¹⁴	MEDLINE	Jan-00	Feb-09	CT, MRI, EUS	Published in English, sufficient data for 2 x 2, surgical confirmation	Results not reported on a per-patient basis	CT: 12, MRI: 4, EUS: 8, total: 16	CT: 694, MR: 143, EUS: 368, total: 797	None	Pooled sensitivity, specificity, DOR, AUC using MetaDiSc;
Wang et al. 2013 ⁵	Pubmed, EMBASE, Cochrane	No limit	Dec-12	Standalone PET, PET/CT	Intravenous FDG, sufficient data for 2 x 2, pathologic confirmation and/or 6 month clinical follow-up, N ≥10	Non-primary cancer, pre-operative radiotherapy or chemotherapy	PET/CT: 1, total: 39	50	None	Pooled sensitivity and specificity using Stata
Zhao et al. 2009 ¹⁵	MEDLINE, PubMed	Not reported	Not reported	CT (includes single slice)	Published in English, pathologic confirmation, sufficient data for 2x2	Incomplete reporting	18	1,201	None	Pooled sensitivity, specificity, and DOR; summary ROC

Table C-4. Key Question 2a systematic reviews: published results

Study	Modality	Method	Patient Subgroup	Diagnostic Decision	N Studies	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy	Significant Heterog.	Comment
Li et al. 2013 ¹⁴	CT (includes single slice)	All	All	Vascular invasion	12	73% (67%-79%)	95% (93%-97%)		Yes	
Li et al. 2013 ¹⁴	CT	Multi-slice	All	Vascular invasion	4	80% (70%-89%)	97% (93%-100%)		Not reported	
Zhao et al. 2009 ¹⁵	CT	Includes single-slice	All	Vascular invasion	19	77% (72%-81%)	81% (78%-85%)		Yes	
Zhao et al. 2009 ¹⁵	CT	2004–2008 studies	All	Vascular invasion	5	85% (78%-91%)	82% (74%-88%)		Yes	
Li et al. 2013 ¹⁴	MRI	All	All	Vascular invasion	4	63% (48%-77%)	93% (86%-98%)		Yes	
Wang et al. 2013 ⁵	PET/CT	All	All	Liver metastasis	1	82% (48%-98%)	97% (87%-100%)			
Wang et al. 2013 ⁵	PET/CT	All	All	Nodal metastasis	0	No data	No data			

Comparative Accuracy Studies

Table C-5. General study information of comparative accuracy studies

Study	Country	Name of Clinic(s)	Range of Dates When Patients Received Imaging Tests	Prospective or Retrospective	Funding Source and Disclosed Potential Conflicts of Interest
Fang et al. 2012 ¹⁶	China	Southwest Hospital of the Third Military Medical University, and Zhujiang Hospital of Southern Medical University	November 2008 to August 2010	Prospective	The National High Technology Research and Development Program of China, the Natural Science Foundation of Guangdong Province, the Science and Technology Project of Guangzhou City, Guangdong Province and the Ministry of Education of P. R. China, Guangdong Province and the Chinese Academy of Sciences, the Science and Technology Project of Guangdong Province, and National Natural Science Foundation of China. No declared conflicted of interest, however the authors had developed and patented one of technologies being assessed (Medical Image Three-Dimensional Visualization System MI-3DVS). "There has been no industry or pharmaceutical support."
Herrmann et al. 2012 ¹⁷	Germany	Universität München	September 2008 and April 2009	prospective	NR
Tellez-Avila et al. 2012 ¹⁸	Mexico	Instituto Nacional de Ciencias Medicas y Nutrition Salvador Zubiran, Mexico City, Mexico	March 2005– March 2010	Prospective	No funding source reported. Authors declare no conflict of interest
Holzapfel et al. 2011 ¹⁹	Germany	Technische Universitaet Muenchen	NR	Prospective	NR
Koelblinger et al. 2011 ²⁰	Austria	Medical University of Vienna	September 2006 to November 2007	Prospective	All nine authors stated explicitly that they had no financial activities to disclose related to the article, and no financial activities to disclose not related to the article, and no other relationships to disclose

Table C-5. General study information of comparative accuracy studies (continued)

Study	Country	Name of Clinic(s)	Range of Dates When Patients Received Imaging Tests	Prospective or Retrospective	Funding Source and Disclosed Potential Conflicts of Interest
Motosugi et al. 2011 ²¹	Japan	University of Yamanashi	March 2008 to June 2010	Retrospective	NR
Rao et al. 2011 ²²	China	Zhongshan Hospital, Fudan University and Shanghai Medical Imaging Institute	NR	Retrospective	NR
Shami et al. 2011 ²³	USA	University of Virginia Health System	NR	Prospective	NR
Takakura et al. 2011 ²⁴	Japan	Jikei University School of Medicine	October 2007 to September 2009	NR	NR
Imai et al. 2010 ²⁵	Japan	Kyoto University	August 2005 to July 2008	Retrospective	"No author has any conflict of interest"
Lee et al. 2010 ²⁶	South Korea	Ewha Women's University	January 2003 to June 2005	Retrospective	"There is no actual or potential conflict of interest for all authors in this manuscript"
Kauhanen et al. 2009 ²⁷	Finland	Turku University Hospital	September 2006 to October 2007	Prospective	Supported by National Graduate School of Clinical Investigation of Final, and a hospital grant. No statements about conflicts of interest.
Farma et al. 2008 ²⁸	USA	H. Lee Moffitt Cancer Center and Research Institute	January 2006 to December 2007	Retrospective	NR
Saif et al. 2008 ²⁹	USA	Yale University School of Medicine	May 2003 to March 2004	Prospective	"Conflicts of interest: None to declare"
Schick et al. 2008 ³⁰	Germany	Muenster University Hospital	July 2005 to February 2007	Prospective	NR
Casneuf et al. 2007 ³¹	Belgium	Gent	October 2004 to April 2006	Prospective	NR
Tamm et al. 2007 ³²	USA	University of Texas MD Anderson Cancer Center	NR	Retrospective	NR
Mehmet Ertuk et al. 2006 ³³	Japan	University of Yamanashi	January 2003 to October 2004	Retrospective	NR
Heinrich et al. 2005 ³⁴	Switzerland & Austria	University Hospital of Zurich & Internal Medicine Landeskrankenhaus Feldkirch, Austria	June 2001 to April 2004	Prospective	NR
Agarwal et al. 2004 ³⁵	USA	MD Anderson Cancer Center	November 2000 to November 2001	Retrospective	NR

Table C-5. General study information of comparative accuracy studies (continued)

Study	Country	Name of Clinic(s)	Range of Dates When Patients Received Imaging Tests	Prospective or Retrospective	Funding Source and Disclosed Potential Conflicts of Interest
DeWitt et al. 2004 ³⁶	USA	Indiana University Medical Center	July 2000 to October 2002	Prospective	Two grants from the American Society of Gastrointestinal Endoscopy, and 1 grant from the NIDDK. Disclosed potential COI: 2 authors had grants from ASGE. Stated “the funding sources had not role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication”.
Lemke et al. 2004 ³⁷	Germany	NR	August 1999 to December 2001	Prospective	Supported by a grant from the Deutsche Forschungsgemeinschaft Graduiertenkolleg 331 and in part by the National Science Foundation (grant EIA-0104114
Soriano et al. 2004 ³⁸	Spain	University of Barcelona	Octobe 1995 to March 2000	Prospective	The work was supported by grants from Fondo de Investigaciones Sanitarias and Ministerio de Ciencia y Tecnologia and the Agencia d'Avaluacio de Tecnologia Medica of the Gernalitat de Catalunya and from Institute de Salud Carols III
Rieber et al. 2000 ³⁹	Germany	Multicenter study - 5 German Institutions participated	NR	Prospective	NR

Table C-6. Patient characteristics of comparative accuracy studies

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Fang et al. 2012 ¹⁶	Confirmed pancreatic or periampullary neoplasms and had received both imaging tests being compared, did not have distant organ metastases, and had undergone surgery	57	81% (46/57)	57.9	43 pancreatic ductal adenocarcinoma of the head, 14 pancreatic ductal adenocarcinoma of the body/tail	The study also included some patients with periampullary cancer, but data were provided specifically for pancreatic cancer. Patient characteristics are based on all enrolled.
Herrmann et al. 2012 ¹⁷	Pancreatic tumours suspicious for malignancy and scheduled for resective surgery	44	36% (16/44)	median age 65±12 years, range 34–86 years		
Tellez-Avila et al. 2012 ¹⁸	Referred because of pancreatic lesion	50	54% (27/50)	61±11.5 years	17/19 patients with adequate tissue samples by EUS. Tissue sampling not attempted in 31 patients. After surgery, histological vascular invasion was demonstrated in 18 patients, vein invasion in 11, and arterial invasion in 9.	

Table C-6. Patient characteristics of comparative accuracy studies (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Holzapfel et al. 2011 ¹⁹	Potentially resectable as seen by MDCT, received diffusion weighted MRI	31	48% (15/31)	61.4 (range 32–84)	23 pancreatic ductal adenocarcinoma, 1 acinar cell carcinoma, 1 neuroendocrine carcinoma, 1 benign IPMN, 1 malignant IPMN, 1 cholangiocarcinoma, 1 papillary carcinoma, 2 focal chronic pancreatitis	
Koelblinger et al. 2011 ²⁰	Informed consent, suspected of having pancreatic cancer, referred to the group of surgeons at the institution, no contraindications to CT/MRI, no time constraints, accepted enrollment, contacted sufficiently soon	89	54% (48/89)	65.5	43 pancreatic adenocarcinoma, 4 ampullary carcinoma, 7 metastases, 1 neuroendocrine tumor, 1 cystadenoma, 9 cystic tumor, 4 inflammatory pseudotumor, 1 focal steatosis, 26 normal pancreas	
Motosugi et al. 2011 ²¹	Patients underwent both dynamic CT and MR cholangio-pancreatography with gadoxetic acid enhancement performed within 1 month, underwent follow-up CT or MR imaging more than 6 months after initial examination	100	47% (47/100)	Men: 67.5 (SD 10.6); Women: 68.2 (SD 10.6)	54 pancreatic carcinoma, 14 biliary stone and/or adenomyomatosis of the gallbladder, 10 biliary carcinoma, 4 gallbladder carcinoma, 3 liver metastasis from colon carcinoma, 6 intraductal papillary mucinous neoplasm of the pancreas, 9 no evidence of disease in the abdomen	

Table C-6. Patient characteristics of comparative accuracy studies (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Rao et al. 2011 ²²	Evidence of small (≤ 2 cm) pancreatic solid tumor	46	54% (25/46)	57 (range 22–81)	18 pancreatic ductal adenocarcinoma, 13 neuroendocrine tumor, 8 metastases (primary cancer not reported but probably pancreatic cancer), 5 solid pseudopapillary tumor, 2 intrapancreatic accessory spleen	
Shami et al. 2011 ²³	Underwent both MRI and EUS-FNA for the workup of pancreatic cancer	127	44% (56/127)	66	All had pancreatic cancer; specific diagnoses not reported	
Takakura et al. 2011 ²⁴	Patients with pancreatic duct dilatations over 3 mm as visualized by MRCP, who underwent both DWI and MDCT	83	27% (22/83)	37–91 years	Pancreatic cancer (presumably adenocarcinoma), IPMN, cholangio (bile duct), adeno of duodenum (papilla of Vater)	
Imai et al. 2010 ²⁵	Diagnosed with invasive ductal adenocarcinoma of pancreas during a time range, no other pancreatic malignancies, underwent preoperative CT and MRI and PET	119	51% (61/119)	65 (range 32–85)	79 pancreatic adenocarcinoma head only, 23 pancreatic adenocarcinoma body only, 5 pancreatic adenocarcinoma tail only, 1 pancreatic adenocarcinoma head + body, 10 pancreatic adenocarcinoma body + tail, 1 pancreatic adenocarcinoma head+body+tail	Comparative accuracy data only reported for the 69/119 who received all three imaging tests CT MRI PET

Table C-6. Patient characteristics of comparative accuracy studies (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Lee et al. 2010 ²⁶	Underwent surgery for pancreatic adenocarcinoma, surgical and pathological findings were available for correlation with imaging tests	56	46% (26/56)	60.9 (range 37–76)	56 pancreatic adenocarcinoma	
Kauhanen et al. 2009 ²⁷	Suspicion of pancreatic malignancy based on ultrasound and/or CT, or suspicion of malignant biliary stricture based on ERCP, no hepatocellular carcinoma, underwent PET/CT and MRI and 64-slice MDCT	38	50% (19/38)	62.6	17 pancreatic adenocarcinoma, 3 neuroendocrine tumor, 4 chronic pancreatitis, 5 benign cystic lesion, 1 malignant cystic lesion, 2 fibrosis, 6 normal pancreas	
Farma et al. 2008 ²⁸	Patients referred to center with a presumed pancreatic neoplasm and who had preoperative PET/CT scans, only patients with pancreatic lesions	82	48% (39/82)	Median: 69 (24 to 88)	65 pancreatic cancer, 17 IPMNs	
Saif et al. 2008 ²⁹	Suspected pancreatic cancer or focal lesion in the pancreas, and had both CT and PET/CT	12	25% (3/12)	61 (range 43–74)	11 malignant pancreatic adenocarcinoma, 1 benign	

Table C-6. Patient characteristics of comparative accuracy studies (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Schick et al. 2008 ³⁰	Solid pancreatic masses of unknown etiology, did not have known pancreatic cancer or known metastases, able to complete the exam, no mental retardation, informed consent	46	30% (14/46)	61.7 (range 31 to 87)	22 ductal adenocarcinoma, 1 adenocarcinoma of the ampulla of Vater, 1 neuroendocrine carcinoma, 1 cholangiocellular carcinoma, 1 metastasis from breast cancer, 1 GIST in duodenum, 14 chronic pancreatitis, 2 pseudocyst with blood/necrotic tissue, 2 bile duct stenosis, 1 focal tuberculosis	
Casneuf et al. 2007 ³¹	Referred for PET/CT for suspected pancreatic disease	34	47% (16/34)	61	18 adenocarcinoma, 4 neuroendocrine tumor, 3 unknown pancreatic tumor, 6 pancreatitis, 3 cystadenoma.	Age was estimated by the EPC based on separately-reported medians of 63 for the 25 positives and 58 for the 9 negatives. The study reported another 12 patients who were included for assessment of recurrence; these patients' data were not extracted.

Table C-6. Patient characteristics of comparative accuracy studies (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Tamm et al. 2007 ³²	1) Clinical suspicion of pancreatic cancer, 2) had undergone both dual-phase MDCT and EUS, 3) MDCT had shown either definite or questionable tumor, or MDCT resulted in a high clinical suspicion of a pancreatic mass, 4) MDCT did NOT show a cystic mass or hypervascular mass suggestive of a neuroendocrine tumor, 5) either clear histopathological proof of true status OR at least 9 months clinical followup after negative MDCT or negative EUS-FNA	117	46% (54/117)	69	95 adenocarcinoma, 2 extrahepatic cholangiocarcinoma, 1 intraductal papillary mucinous neoplasm without a cystic component, 1 ampullary carcinoma, 10 chronic pancreatitis, 1 benign pancreatic duct stricture, 3 benign common bile duct stricture, 1 choledochal cyst	
Mehmet Ertuk et al. 2006 ³³	Either 1) underwent surgery for pancreatic adenocarcinoma and had had both multiphasic MDCT and MRI prior to surgery, or 2) did not have pancreatic carcinoma and underwent CT and MRI during the same period of time	45	56% (25/45)	67.4 (range 42 to 85)	14 head adenocarcinoma, 6 body adenocarcinoma, 4 tail adenocarcinoma, 3 elevated CA 19-9 but no adenocarcinoma, 5 acute pancreatitis, 7 chronic pancreatitis, 6 IPMN.	Age calculated based on weighted average of reported mean ages of positives and negatives

Table C-6. Patient characteristics of comparative accuracy studies (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Heinrich et al. 2005 ³⁴	Patients with a focal lesion in the pancreas or with clinical suspicion of pancreatic cancer was eligible for this analysis	59	49% (29/59)	Median: 61 (40 to 80)	43 ductal adenocarcinoma, 1 acinuscell carcinoma, 1 Neuroendocrine cancer, 1 Metastasis from colon cancer, 1 serous microcystic adenoma, 1 high-grade epithelial dysplasia, 1 focal tuberculosis, 3 chronic pancreatitis (pseudotumor); 7 no definitive histologic diagnosis was available	
Agarwal et al. 2004 ³⁵	If clinical suspicion of pancreatic cancer was based on: obstructive jaundice with biliary stricture seen on ERCP (n=47), suspected pancreatic mass on CT (n=19), and two or more episodes of acute pancreatitis in 6 months without predisposing factors (n=15)	81	51% (41/81)	66.4 (SD 10.5)	71 malignant and 10 benign. Of the 71 malignant tumors: 58 were located in the pancreatic head, five in the uncinate process, and eight in the neck, body or tail of the pancreas)	

Table C-6. Patient characteristics of comparative accuracy studies (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
DeWitt et al. 2004 ³⁶	1) Clinically suspected or recently diagnosed solid or cystic pancreatic cancer with the past 8 weeks, 2) agreed to undergo EUS and CT and surgery (if necessary), 3) had not already undergone ERCP or EUS for suspected pancreatic cancer; 4) did not decline or remain undecided about surgical intervention; 5) were not referred by surgeons outside their hospital system; 6) were not pregnant; 7) were not incarcerated; 8) could independently provide informed consent; 9) were not considered high surgical risk (not ASA class III IV or V); 10) had known or suspected periampullary masses; 11) had cholangiocarcinoma; 12) had cancer with suspected locally advanced arterial involvement or metastatic disease detected by previous imaging studies.	104	43% (45/104)	64	28 unresectable pancreatic cancer determined after surgery, 25 resectable pancreatic cancer, 5 chronic pancreatitis, 1 benign intraductal papillary mucinous tumor, 1 macrocystic serious [sic] cystadenoma, 1 benign neuroendocrine tumor, 1 accessory spleen, 1 ampullary cancer, 9 benign resectable focal pancreatic masses without vascular invasion, 26 pancreatic adenocarcinoma determined without surgery, 1 neuroendocrine carcinoma determined without surgery, 2 suspected unresectable gall bladder carcinoma or hepatoma, 3 no mass, 1 suspected liver abscess, 8 benign disease	–

Table C-6. Patient characteristics of comparative accuracy studies (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Lemke et al. 2004 ³⁷	Suspected pancreatic lesion	104	51% (53/104)	Median 64 (Range 23–84)	(See comments) 57 adenocarcinoma, 5 carcinoma of papilla of Vater, 1 bile duct carcinoma, 1 neuroendocrine tumor, 28 chronic pancreatitis, 5 papillary adenoma, 3 other benign lesions	Final diagnoses: 53 surgical resection, 25 exploratory surgery, 16 percutaneous needle aspiration biopsy, 10 clinical follow-up
Soriano et al. 2004 ³⁸	Had pancreatic or ampullary carcinoma, fit for surgery, confirmed neoplasm, gave consent, no massive metastasis precluding surgery, at least 3 imaging techniques could be performed	62	47% (29/62)	65	42 Pancreas head cancer, 6 pancreas body cancer, 4 pancreas tail cancer, 10 ampullary cancer	
Rieber et al. 2000 ³⁹	known or suspected pancreatic malignancy, Minimum age of 18 years, patient consciousness and cooperation, written informed consent, free withdrawal from the study, no participation in drug administration phase of another trial	20	30% (6/20)	Avg. 62 (range 34–88)	8 pancreatic adenocarcinoma, 10 chronic pancreatitis, 2 stenosing papillitis	

Table C-7. General test details of comparative accuracy studies

Study	Imaging Tests of Interest	Order of Tests Performed	Elapsed Time Between Imaging Tests	Number of Test Readers per Scan	Prior Experience of These Readers With This Imaging Test	Other Reported Details About the Readers	Reference Standard Determination Based on:
Fang et al. 2012 ¹⁶	CT angiography with 3D reconstruction vs. without 3D reconstruction	CTA was always first	None; the same images were used. 3D reconstruction was performed by software	2 (not the same as those who read the other test)	NR	NR	Intraoperative exam
Herrmann et al. 2012 ¹⁷	MDCT vs. PET/CT	Not clear. FDG PET CT, FLT PET and diagnostic CT were performed in different subgroups of patients. Some patients came with diagnostic CTs prior to treatment at this institution and others had it afterwards.	One day between FLT and FDG. No specified time between FDG and diagnostic CT	3	"board certified"	board certified nuclear medicine physicians and "board certified" radiologist	Cytology/histology

Table C-7. General test details of comparative accuracy studies (continued)

Study	Imaging Tests of Interest	Order of Tests Performed	Elapsed Time Between Imaging Tests	Number of Test Readers per Scan	Prior Experience of These Readers With This Imaging Test	Other Reported Details About the Readers	Reference Standard Determination Based on:
Tellez-Avila et al. 2012 ¹⁸	MDCT vs. EUS-FNA	MDCT was always first	NR	2	"Certified Radiologists"	NR	Pathologic specimen required to confirm imaging results. Accuracy of study to determine presence of vascular invasion preoperatively was the outcome measure. Reviewed presence of histologic vascular invasion (artery/vein). Vascular invasion is considered good predictor for poor prognosis after local resection
Holzapfel et al. 2011 ¹⁹	MDCT vs. MRI	MDCT was always first	Mean 7.5 days, range 1–16 days	2	NR	2 radiologists	Intraoperative surgical and ultrasound findings in all 31 patients, as well as histopathology in 11 of 31

Table C-7. General test details of comparative accuracy studies (continued)

Study	Imaging Tests of Interest	Order of Tests Performed	Elapsed Time Between Imaging Tests	Number of Test Readers per Scan	Prior Experience of These Readers With This Imaging Test	Other Reported Details About the Readers	Reference Standard Determination Based on:
Koelblinger et al. 2011 ²⁰	MDCT vs. MRI	NR	At most one week	2	At least 10 years' experience in both abdominal CT and MRI	2 gastrointestinal radiologists	Diagnosis: Histology in 59/89 (66%) overall (the 59 were comprised of 33 surgical histology and 26 who had either CT-guided or EUS-guided biopsy), and clinical followup of at least 6 months in the remaining 30 patients. Other clinical decisions: Surgical histology

Table C-7. General test details of comparative accuracy studies (continued)

Study	Imaging Tests of Interest	Order of Tests Performed	Elapsed Time Between Imaging Tests	Number of Test Readers per Scan	Prior Experience of These Readers With This Imaging Test	Other Reported Details About the Readers	Reference Standard Determination Based on:
Motosugi et al. 2011 ²¹	MDCT vs. MRI	MDCT was always first	NR	3	Reader had only a small amount of experience in abdominal MRI while readers 2 and 3 had been in the abdominal subgroup for more than 5 years. Reader 1 interpreted far fewer abdominal MRIs in daily work compared with the other two readers.	CT and MRIs in patients with and without pancreatic carcinoma were interpreted independently and in random order by the three readers. More than 1 week of time interval was set between the reading sessions of images to reduce recall bias. Each reader graded the presence (or absence of pancreatic carcinoma on a 5 point confidence scale. Readers were blinded to the clinical histories and final diagnoses. Images were also interpreted for the presence of liver metastases in patients with pancreatic carcinoma. Each reader graded the presence (or absence) of liver mets on a 5 point scale. If any false-positive or false-negative results were observed in any reader's interpretation, the study coordinators assessed the reason for the misinterpretation by reviewing the images.	For diagnosis: 54 patients with pancreatic cancer confirmed at surgery (23), transendoscopic biopsy (24), or brush cytology of pancreatic duct (7). 46 patients without pancreatic cancer were confirmed at follow-up CT or MRI performed more than 6 months after initial examination. For metastases: 15 of 56 patients with pancreatic cancer were found to have 62 liver metastases: 6 lesions found by pathologic results, 49 lesions showing hypoattenuation on post contrast CT or MRI that had increased in size at follow-up exam, 7 lesions that had disappeared or decreased in size after chemotherapy at the follow-up exam
Rao et al. 2011 ²²	MDCT vs. MRI	MDCT was "usually the first choice"	NR	2	At least 5 years' experience	2 gastrointestinal radiologists	Histopathology
Shami et al. 2011 ²³	EUS-FNA vs. MRI	NR	NR	1	a "qualified" radiologist	NR	Surgical histology

Table C-7. General test details of comparative accuracy studies (continued)

Study	Imaging Tests of Interest	Order of Tests Performed	Elapsed Time Between Imaging Tests	Number of Test Readers per Scan	Prior Experience of These Readers With This Imaging Test	Other Reported Details About the Readers	Reference Standard Determination Based on:
Takakura et al. 2011 ²⁴	MDCT vs. MRI	Not specified	No more than 90 days between tests	4	"Experienced"	2 gastroenterology fellows, 2 radiologists	cytology for some and clinical follow up for others
Imai et al. 2010 ²⁵	MDCT vs. MRI	NR	NR	2 or more	"Experienced"	Radiologists	Surgery in 102, probe laparotomy in 17. Did not report this delineation specifically for the 69 patients in whom imaging accuracy were reported
Lee et al. 2010 ²⁶	MDCT vs. MRI	Random order	Mean 3.8 days (range 0–14)	2	Both readers had completed a subspecialty fellowship in gastrointestinal radiology	Two radiologists	Surgical findings in all
Kauhanen et al. 2009 ²⁷	MDCT vs. MRI vs. PET/CT	NR	MRI was within two weeks of MDCT and PET/CT; MDCT and PET/CT were same-day	1 for MDCT and MRI, 2 for PET/CT	NR	Abdominal radiologist. Used one reader from a different institution to prevent recall bias.	Diagnosis: Surgery in 23, biopsy in 3, autopsy in 3, and clinical followup in 9 (minimum followup 12 months). Metastases: Surgical findings in 7/14, and histopathology in the other 7
Farma et al. 2008 ²⁸	MDCT vs. PET/CT	MDCT was always first	NR	NR	NR	all patients were discussed in the multidisciplinary gastrointestinal tumor board mtg prior to definitive treatment planning	All patients had either a percutaneous or endoscopic core needle, or fine needle aspiration biopsy confirming histologic diagnosis.
Saif et al. 2008 ²⁹	MDCT vs. PET/CT	MDCT was always first	No time elapsed	NR	NR	Nuclear medicine physicians and radiologists	Pathology in 6, clinical followup in the other 6

Table C-7. General test details of comparative accuracy studies (continued)

Study	Imaging Tests of Interest	Order of Tests Performed	Elapsed Time Between Imaging Tests	Number of Test Readers per Scan	Prior Experience of These Readers With This Imaging Test	Other Reported Details About the Readers	Reference Standard Determination Based on:
Schick et al. 2008 ³⁰	EUS-FNA vs. PET/CT	PET/CT was always first	Within 3 weeks	2	EUS-FNA: NA. PET/CT: Fused data were read by 2 readers in consensus. 1 was a board-certified nuclear medicine physician experienced in PET interpretation, and the other was a board-certified radiologist experienced in CT analysis.	EUS-FNA: NA. PET/CT: 1 nuclear medicine physician and 1 radiologist	Histology in 43/46 patients and clinical followup of at least 12 months in 3/46
Casneuf et al. 2007 ³¹	MDCT vs. PET/CT	MDCT was always first	NR	1 for MDCT, 2 for PET/CT	NR	Identified by name	31/34 histological findings, 3/34 clinical course
Tamm et al. 2007 ³²	MDCT vs. EUS-FNA	MDCT was always first	NR	1	NR	3 radiologists	Histopathology from either surgical findings or biopsy, or if negative biopsy, then clinical followup of at least 9 months
Mehmet Ertuk et al. 2006 ³³	MDCT vs. MRI	Order not reported for patients who did not have pancreatic adenocarcinoma. For those who did, MDCT was performed first for 13/24 and MRI was performed first for 11/24	Time difference not reported for those without pancreatic adenocarcinoma. For those with it, at most one week	3	"Experienced"	3 abdominal radiologists	Surgery in the 24 known adenocarcinomas, and for the 21 negatives it was surgery in 3 and clinical followup of at least 12 months in the remaining 18

Table C-7. General test details of comparative accuracy studies (continued)

Study	Imaging Tests of Interest	Order of Tests Performed	Elapsed Time Between Imaging Tests	Number of Test Readers per Scan	Prior Experience of These Readers With This Imaging Test	Other Reported Details About the Readers	Reference Standard Determination Based on:
Heinrich et al. 2005 ³⁴	MDCT vs. PET/CT	MDCT was always first	Median: 10 days	4	NR	At least 2 nuclear medicine physicians and radiologists. All CT images were viewed separately to identify additional lesions without FDG uptake using soft tissue, lung, and bone window leveling	EUS-FNA of primary tumor and FNA of metastatic lesions, serial CA 19-9 levels, and diagnostic laparoscopy
Agarwal et al. 2004 ³⁵	MDCT vs. EUS-FNA	MDCT was always first	NR	NR	NR	CT: radiologists who specialize in body imaging. EUS-FNA: Cytologist could make the preliminary diagnosis	Definitive cytology, surgical pathology, or development of metastatic disease
DeWitt et al. 2004 ³⁶	MDCT vs. EUS-FNA	EUS-FNA was always first	At most one week	3	MDCT: they were "Experienced." EUS-FNA: All had at least 1000 prior EUS exams	3 gastroenterologists	For diagnosis: Either 1) intraoperative exam or 2) EUS-FNA or previously obtained cytology and subsequent clinical follow-up. For resectability and T staging: Intraoperative exam (only R0) was considered resectable.
Lemke et al. 2004 ³⁷	MDCT vs. PET/CT	MDCT was always first	Median 3 days (range 1-6)	2	"Experienced"	Radiologists reviewed images using standardized questionnaires	Surgical resection (53), exploratory surgery (25), percutaneous needle aspiration biopsy (16), and clinical follow-up (10)
Soriano et al. 2004 ³⁸	MDCT vs. MRI	Pseudo-random order depending on the available of test technologies	NR	NR	NR	NR	Surgical findings in all
Rieber et al. 2000 ³⁹	MDCT vs. MRI	MDCT performed first	NR	3	NR	Radiologists	histological findings for all cases

Table C-8. MDCT details of comparative accuracy studies

Study	MDCT: 4 vs. 16 vs. 64 Detector Row or Other	MDCT: Slice Thickness (if NR, Then Record Machine Name)	MDCT: Whether Reformats Used (e.g., Coronal, Sagittal) or Only Axial	MDCT: Contrast Y or N	MDCT: Type of Contrast	MDCT: Phases of Enhancement Dynamic vs. Routine; Arterial/Portal Venous/Equilibrium Means Dynamic
Fang et al. 2012 ¹⁶	64	0.67 mm	Y	Y	80–100 mL Iopamiro	Dual phase
Herrmann et al. 2012 ¹⁷	NR	NR	NR	NR	NR	NR
Tellez-Avila et al. 2012 ¹⁸	16 or 64	3mm–5mm	Coronal reformatted images	Y	120 mL of Conray was given 45 seconds before CT examination. 40 mL of ioditrac M60 was diluted in 1,000 mL of water and given to all patients orally 1 hour before CT imaging	Dynamic
Holzappel et al. 2011 ¹⁹	64	0.6 mm	Y	Y	120 mL Imeron 300	Dual-phase
Koelblinger et al. 2011 ²⁰	64	0.6 mm	Y	Y	150 mL Iomeprol	Dynamic
Motosugi et al. 2011 ²¹	16	5 mm	NR	Y	300 mg/mL Omnipaque 300	Dynamic
Rao et al. 2011 ²²	16	0.75 mm and 0.625 mm	Y	Y	300mg Ultravist	Three-phase
Shami et al. 2011 ²³	-	-	-	-	-	-
Takakura et al. 2011 ²⁴	64	Definition, Siemens, Erlangen, Germany	Not specified	Yes	(Iopamiron 370, Bayer Schering Pharma, Berlin, Germany)	Dual (arterial and delayed presumably from 90 second delay)
Imai et al. 2010 ²⁵	64	0.5 mm	NR	Y	Iopamiron 2 mL/kg	Dual-phase
Lee et al. 2010 ²⁶	4	1.25 mm	Y	Y	Iopromide 150 mL	Dual phase
Kauhanen et al. 2009 ²⁷	64	5 mm	N	Y	Iomerol 400 mg/mL 1.5mL contrast/kg	Four-phase
Farma et al. 2008 ²⁸	NR	NR	NR	NR	NR	NR
Saif et al. 2008 ²⁹	4	1 to 3 mm	N	Yes	Gastrograffin	NR
Schick et al. 2008 ³⁰	16	0.75 mm upper abdomen	Y	Y	140 mL Iomeprol	Dual-phase
Casneuf et al. 2007 ³¹	16	3 mm	NR	Y	140mL Iodixanol 320 mg iodine per mL	Venous
Tamm et al. 2007 ³²	4	2.5 mm first phase, 5 mm second phase	N	Y	150mL Ioversol 350 mg Iodine/mL	Dual-phase

Table C-8. MDCT details of comparative accuracy studies (continued)

Study	MDCT: 4 vs. 16 vs. 64 Detector Row or Other	MDCT: Slice Thickness (if NR, Then Record Machine Name)	MDCT: Whether Reformats Used (e.g., Coronal, Sagittal) or Only Axial	MDCT: Contrast Y or N	MDCT: Type of Contrast	MDCT: Phases of Enhancement Dynamic vs. Routine; Arterial/Portal Venous/Equilibrium Means Dynamic
Mehmet Ertuk et al. 2006 ³³	16	0.5 mm	Y	Y	350 mg/mL Iomeron	Three-phase
Heinrich et al. 2005 ³⁴	4	5 mm	Axial	Y	Oral contrast	NR
Agarwal et al. 2004 ³⁵	NR	1.25 mm (parenchymal phase); 2.5 mm (portal phase)	NR	Y	150 mL of nonionic contrast material (Optiray 320, Mallinckrodt Inc., St. Louis, MO)	Dynamic
DeWitt et al. 2004 ³⁶	4	first phase 1.3 mm effective section thickness, second phase 3.2 mm effective section thickness	Sometimes (NR percentage of procedures)	Y	150 mL Isovue-300, 300 mg Iodine/mL	Dual phase
Lemke et al. 2004 ³⁷	NR	NR	NR	Y	100 mL iopromide (Ultravist 370, Schering AG)	Dynamic
Soriano et al. 2004 ³⁸	4	8mm	Y	Y	Iohexol 64.75g	Dual-phase
Rieber et al. 2000 ³⁹	NR	NR	NR	Y	150 mL iopromide (Ultravist 300, Schering, Berlin)	Dynamic

Table C-9. EUS-FNA details of comparative accuracy studies

Study	EUS FNA Technology Name for EUS	EUS-FNA Needle Type	EUS-FNA Needle Size	How Many Patients Received FNA?	Other EUS-FNA Details
Fang et al. 2012 ¹⁶	-	-	-	-	-
Herrmann et al. 2012 ¹⁷	-	-	-	-	-
Tellez-Avila et al. 2012 ¹⁸	Linear GF UCT-140 echoendoscope (Olympus, American Corp, Melville, NY) with an Aloka console SSD 5500. Used with an 8 cm long 22 or 19- gauge EchoTip Needle	EchoTip Needle	8 cm long 22- or 19- gauge EchoTip needle	21 but only 17/19 had adequate tissue samples for histologic evaluation	-
Holzapfel et al. 2011 ¹⁹	-	-	-	-	-
Koelblinger et al. 2011 ²⁰	-	-	-	-	-
Motosugi et al. 2011 ²¹	-	-	-	-	-
Rao et al. 2011 ²²	-	-	-	-	-
Shami et al. 2011 ²³	Olympus GF-UCT140 or GF-UC140P	NR	NR	NR	NR
Takakura et al. 2011 ²⁴	-	-	-	-	-
Imai et al. 2010 ²⁵	-	-	-	-	-
Lee et al. 2010 ²⁶	-	-	-	-	-
Kauhanen et al. 2009 ²⁷	-	-	-	-	-
Farma et al. 2008 ²⁸	-	-	-	-	-
Saif et al. 2008 ²⁹	-	-	-	-	-
Schick et al. 2008 ³⁰	Hitachi FG 38vx	NR	22 gauge	29	Transduodenal approach for pancreatic head lesions, or transgastric approach for body/tail lesions
Casneuf et al. 2007 ³¹	-	-	-	-	-

Table C-9. EUS-FNA details of comparative accuracy studies, (continued)

Study	EUS FNA Technology Name for EUS	EUS-FNA Needle Type	EUS-FNA Needle Size	How Many Patients Received FNA?	Other EUS-FNA Details
Tamm et al. 2007 ³²	Olympus EUM-30 and Pentax FG-32A	NR	NR	NR	NR
Mehmet Ertuk et al. 2006 ³³	-	-	-	-	-
Heinrich et al. 2005 ³⁴	-	-	-	-	-
Agarwal et al. 2004 ³⁵	Olympus EUM-30 and Pentax FG-32A	Echo-tip (Wilson Cook, Winston Salem, NC)	NR	81	EUS-FNA was considered positive only if a definitive cytologic diagnosis of malignancy could be made with fine needle aspirates.
DeWitt et al. 2004 ³⁶	Either Olympus GF-UM130 or Pentax GF-36UX or Olympus GF-UC140P	Wilson-Cook Medical	22 gauge	NR	On-site cytopathologist
Lemke et al. 2004 ³⁷	-	-	-	-	-
Soriano et al. 2004 ³⁸	-	-	-	-	-
Rieber et al. 2000 ³⁹	-	-	-	-	-

Table C-10. MRI details of comparative accuracy studies

Study	MRI: Magnet Strength	MRI: Contrast Y or N	MRI: Type of Contrast	MRI: Phases of Enhancement Dynamic vs. Routine; Arterial/Portal Venous/Equilibrium Means Dynamic	MRI: Diffusion-weighted Y or N	MRI: Type of Coil (Body/Pelvic or Endorectal)
Fang et al. 2012 ¹⁶	-	-	-	-	-	-
Herrmann et al. 2012 ¹⁷	-	-	-	-	-	-
Tellez-Avila et al. 2012 ¹⁸	-	-	-	-	-	-
Holzapfel et al. 2011 ¹⁹	1.5 T	N	NA	None	Y	2–6 channel-body-phased array coils anterior and two spine clusters posterior
Koelblinger et al. 2011 ²⁰	3 T (Trio Tim)	Y	0.1 mmol/kg gadobenate dimeglumine	Three-phase	N	Surface coils
Motosugi et al. 2011 ²¹	1.5 T	Y	gadovetic acid (0.025 mmol per kilogram of body weight)	Dynamic	N (diffusion weighted images obtained but not used in this study)	NR
Rao et al. 2011 ²²	1.5 T	Y	30 mL Magnevist	Dynamic	N	NR
Shami et al. 2011 ²³	1.5 T Magnetom Sonata, Symphony and Avanta (Siemens)	Y	10–20 cc gadopentetate dimeglumine	Three-phase	N	Body coil
Takakura et al. 2011 ²⁴	1.5 T	N (not relevant only looking at DWI)	NA	NA	Y	12-channel body and spine matrix coil combination
Imai et al. 2010 ²⁵	1.5 T	N	NA	None	N	NR
Lee et al. 2010 ²⁶	1.5 T	Y	Gadolinium	Dual-phase	N	Body coil
Kauhanen et al. 2009 ²⁷	1.5 T	Y	Gadolinium 0.2 mL/kg	Dynamic	N	Surface coil
Farma et al. 2008 ²⁸	-	-	-	-	-	-
Saif et al. 2008 ²⁹	-	-	-	-	-	-
Schick et al. 2008 ³⁰	-	-	-	-	-	-

Table C-10. MRI details of comparative accuracy studies (continued)

Study	MRI: Magnet Strength	MRI: Contrast Y or N	MRI: Type of Contrast	MRI: Phases of Enhancement Dynamic vs. Routine; Arterial/Portal Venous/Equilibrium Means Dynamic	MRI: Diffusion-weighted Y or N	MRI: Type of Coil (Body/Pelvic or Endorectal)
Casneuf et al. 2007 ³¹	-	-	-	-	-	-
Tamm et al. 2007 ³²	-	-	-	-	-	-
Mehmet Ertuk et al. 2006 ³³	1.5 T	Y	20 mL gadolinium	Three-phase	N	NR
Heinrich et al. 2005 ³⁴	-	-	-	-	-	-
Agarwal et al. 2004 ³⁵	-	-	-	-	-	-
DeWitt et al. 2004 ³⁶	-	-	-	-	-	-
Lemke et al. 2004 ³⁷	-	-	-	-	-	-
Soriano et al. 2004 ³⁸	1.0 T	Y	Gadopentate dimeglumine 0.1 mmol/kg	Dynamic	N	body
Rieber et al. 2000 ³⁹	1.5 T	Y	Mn-DPDP 5 µmol kg(-1)	NR	Y	body

Table C-11. PET/CT details of comparative accuracy studies

Study	PET: Isotope	PET: Mean Dose of Isotope	PET: Uptake Time	Integrated or Superimposed
Fang et al. 2012 ¹⁶	-	-	-	-
Herrmann et al. 2012 ¹⁷	FDG	300–400 MBq	90 min	Integrated
Tellez-Avila et al. 2012 ¹⁸	-	-	-	-
Holzapfel et al. 2011 ¹⁹	-	-	-	-
Koelblinger et al. 2011 ²⁰	-	-	-	-
Motosugi et al. 2011 ²¹	-	-	-	-
Rao et al. 2011 ²²	-	-	-	-
Shami et al. 2011 ²³	-	-	-	-
Takakura et al. 2011 ²⁴	-	-	-	-
Imai et al. 2010 ²⁵	-	-	-	-
Lee et al. 2010 ²⁶	-	-	-	-
Kauhanen et al. 2009 ²⁷	FDG	366 +/- 15 MBq	60 minutes	Integrated
Farma et al. 2008 ²⁸	FDG	296-555 MBq (8-15 mCi)	90 minutes	Integrated
Saif et al. 2008 ²⁹	FDG	10 mCi	60 minutes	Integrated
Schick et al. 2008 ³⁰	FDG	4 MBq/kg	60 minutes	Y
Casneuf et al. 2007 ³¹	FDG	4 MBq/kg	60 minutes	Integrated
Tamm et al. 2007 ³²	-	-	-	-
Mehmet Ertuk et al. 2006 ³³	-	-	-	-
Heinrich et al. 2005 ³⁴	FDG	350 to 450 MBq	60 minutes	Integrated
Agarwal et al. 2004 ³⁵	-	-	-	-
DeWitt et al. 2004 ³⁶	-	-	-	-
Lemke et al. 2004 ³⁷	FDG	5 MBq/kg	60 to 90 minutes	NR
Soriano et al. 2004 ³⁸	-	-	-	-
Rieber et al. 2000 ³⁹	-	-	-	-

Table C-12. Comparative accuracy data for tests of interest in included studies

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Fang et al. 2012 ¹⁶	Resectability without staging	MDCT angiography without 3D reconstruction	MDCT angiography with 3D reconstruction	89.5% (17/19)	78.9% (30/38)	100% (19/19)	100% (38/38)	Yes	Unresectability defined as a positive
Tamm et al. 2007 ³²	Diagnosis	MDCT	EUS-FNA	97% (96/99)	72.2% (13/18)	82.8% (82/99)	94.4% (17/18)	No	For MDCT, the test results are based on a consensus of 3 independent readers. The study also reported results for EUS (tp=98, fp=9, fn=1, tn=9) and stated "to fairly compare EUS with MDCT, we scored only the EUS-FNA biopsy results for the first endoscopic procedure performed at our institution."
Agarwal et al. 2004 ³⁵	Diagnosis	MDCT	EUS-FNA	74.6% (53/71)	70% (7/10)	88.7% (63/71)	100% (10/10)	Yes	MDCT values are based on studies' Spiral CT-1 results - "probable" masses counted as negative

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Agarwal et al. 2004 ³⁵	Diagnosis	MDCT	EUS-FNA	85.9% (61/71)	40% (4/10)	88.7% (63/71)	100% (10/10)	Yes	MDCT values are based on studies' Spiral CT-2 results - "probable" masses counted as positive
DeWitt et al. 2004 ³⁶	Diagnosis	MDCT	EUS-FNA	86.3% (69/80)	62.5% (15/24)	97.5% (78/80)	62.5% (15/24)	Yes	After the two imaging tests, within 3 weeks a surgeon examined the patient and the imaging results to determine eligibility for resection. The 9 patients who were deemed by both tests to have a pancreatic mass but were later found to not have pancreatic cancer were all counted as false positives. Cross-classified data: Actual +, test 1+, test 2+: 68. Actual +, test 1+, test 2-: 1. Actual +, test 1 -, test 2+: 10. Actual +, test 1 -, test 2-: 1. Actual -, test 1 -, test 2-: 15. Actual -, test 1 -, test 2+: 0. Actual -, test 1+, test 2-: 0. Actual -, test 1+, test 2+: 9.

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Koelblinger et al. 2011 ²⁰	Diagnosis	MDCT	MRI	97.7% (42/43)	96.2% (25/26)	97.7% (42/43)	92.3% (24/26)	Yes	These are data for reader 1. Extracted data included those with pancreatic adenocarcinoma (N=43) and those with normal pancreas (N=26).
Koelblinger et al. 2011 ²⁰	Diagnosis	MDCT	MRI	93% (40/43)	96.2% (25/26)	95.3% (41/43)	96.2% (25/26)	Yes	These are data for reader 2. Extracted data included those with pancreatic adenocarcinoma (N=43) and those with normal pancreas (N=26).
Motosugi et al. 2011 ²¹	Diagnosis	MDCT	MRI	94.4% (51/54)	97.8% (45/46)	96.3% (52/54)	97.8% (45/46)	Yes	Reviewer 1 results
Motosugi et al. 2011 ²¹	Diagnosis	MDCT	MRI	96.3% (52/54)	97.8% (45/46)	98.1% (53/54)	97.8% (45/46)	Yes	Reviewer 2 results
Motosugi et al. 2011 ²¹	Diagnosis	MDCT	MRI	96.3% (52/54)	97.8% (45/46)	98.1% (53/54)	97.8% (45/46)	Yes	Reviewer 3 results
Rao et al. 2011 ²²	Diagnosis	MDCT	MRI	84% (21/25)	94.1% (16/17)	87.5% (7/8)	50% (4/8)	Yes	These are the data for reader A. We considered adenocarcinomas and metastasis to be positives, whereas neuroendocrine tumors and solid papillary tumors and intrapancreatic accessory spleens to be negatives.

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Rao et al. 2011 ²²	Diagnosis	MDCT	MRI	96% (24/25)	88.2% (15/17)	100% (8/8)	62.5% (5/8)	Yes	These are the data for reader B. We considered adenocarcinomas and metastasis to be positives, whereas neuroendocrine tumors and solid papillary tumors and intrapancreatic accessory spleens to be negatives.
Takakura et al. 2011 ²⁴	Diagnosis	MDCT	MRI	81.8% (27/33)	88% (44/50)	78.8% (26/33)	88% (44/50)	No	Reported sensitivity and specificity were based on four readers; confidence intervals were calculated as if there had been four times as many patients as there actually were (i.e., the footnote to Table 2 indicates a denominator of 332 even though there were only 83 patients). Prevalence was 39%. We estimated counts for 83 patients based on reported prevalence and accuracy percentages
Kauhanen et al. 2009 ²⁷	Diagnosis	MDCT	MRI	85% (17/20)	66.7% (12/18)	85% (17/20)	72.2% (13/18)	Yes	–
Mehmet Ertuk et al. 2006 ³³	Diagnosis	MDCT	MRI	83.3% (20/24)	85.7% (18/21)	83.3% (20/24)	100% (21/21)	Yes	This is reader 1

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Mehmet Ertuk et al. 2006 ³³	Diagnosis	MDCT	MRI	83.3% (20/24)	90.5% (19/21)	83.3% (20/24)	95.2% (20/21)	Yes	This is reader 2
Mehmet Ertuk et al. 2006 ³³	Diagnosis	MDCT	MRI	83.3% (20/24)	90.5% (19/21)	83.3% (20/24)	100% (21/21)	Yes	This is reader 3
Rieber et al. 2000 ³⁹	Diagnosis	MDCT	MRI	100% (8/8)	75% (9/12)	87.5% (7/8)	75% (9/12)	Yes	-
Herrmann et al. 2012 ¹⁷	Diagnosis	MDCT	PET/CT	88% (22/25)	0% (0/6)	96% (24/25)	16.7% (1/6)	Yes	-
Kauhanen et al. 2009 ²⁷	Diagnosis	MDCT	PET/CT	85% (17/20)	66.7% (12/18)	85% (17/20)	94.4% (17/18)	Yes	-
Saif et al. 2008 ²⁹	Diagnosis	MDCT	PET/CT	91.7% (11/12)	25% (1/4)	100% (11/11)	80% (4/5)	No	These data are per lesion, not per patient

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Casneuf et al. 2007 ³¹	Diagnosis	MDCT	PET/CT	87.5% (21/24)	90% (9/10)	91.7% (22/24)	90% (9/10)	No	Lymph node accuracy data excluded because results not provided for PET/CT. The text conflicted with the table; our extraction is the numbers provided in the text. Table 3a stated that the sensitivity of CT was 92.0%, whereas the text implied 87.5%. Table 3a stated that the sensitivity of PET/CT was 84.0%, whereas the text implied 91.7%. Table 3a stated that the specificity of CT was 88.8%, whereas the text implied 90%. Table 3a stated that the sensitivity of PET/CT was 88.8%, whereas the text implied 90%. Lesions-by-lesion reporting was not extracted because authors did not report denominators for either MDCT or PET/CT.
Heinrich et al. 2005 ³⁴	Diagnosis	MDCT	PET/CT	93.5% (43/46)	23.1% (3/13)	89.1% (41/46)	69.2% (9/13)	Yes	Counts for contrast enhanced CT were based on reported sensitivity and specificity

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Lemke et al. 2004 ³⁷	Diagnosis	MDCT	PET/CT	76.6% (49/64)	63.9% (23/36)	89.1% (57/64)	63.9% (23/36)	No	PET and CT were fused for only 100 of 104 patients, and the data are based only on these 100 patients
Schick et al. 2008 ³⁰	Diagnosis	EUS-FNA	PET/CT	80.8% (21/26)	84.2% (16/19)	88.9% (24/27)	73.7% (14/19)	Yes	One patient did not receive EUS-FNA because other tests made the diagnosis obvious.
Kauhanen et al. 2009 ²⁷	Diagnosis	MRI	PET/CT	85% (17/20)	72.2% (13/18)	85% (17/20)	94.4% (17/18)	Yes	–
DeWitt et al. 2004 ³⁶	Resectability without staging	MDCT	EUS-FNA	64% (18/28)	92% (23/25)	68% (19/28)	88% (22/25)	Yes	This only includes the 53 patients with pancreatic cancer who had surgery. In the data to the left, true unresectability is a “positive,” and true resectability is a “negative.”
Koelblinger et al. 2011 ²⁰	Resectability without staging	MDCT	MRI	75% (6/8)	86.7% (13/15)	75% (6/8)	93.3% (14/15)	Yes	These are data for reader 1. Extracted data included those with pancreatic adenocarcinoma who underwent surgery (N=23). Table 4 in the article reports a resectable case as a positive, but we extracted a resectable as a negative to be consistent in evidence tables.

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Koelblinger et al. 2011 ²⁰	Resectability without staging	MDCT	MRI	62.5% (5/8)	86.7% (13/15)	50% (4/8)	93.3% (14/15)	Yes	These are data for reader 2. Extracted data included those with pancreatic adenocarcinoma who underwent surgery (N=23). Table 4 in the article reports a resectable case as a positive, but we extracted a resectable as a negative to be consistent in evidence tables.
Lee et al. 2010 ²⁶	Resectability without staging	MDCT	MRI	64.7% (11/17)	89.7% (35/39)	41.2% (7/17)	89.7% (35/39)	Yes	These are the data for reader 1.
Lee et al. 2010 ²⁶	Resectability without staging	MDCT	MRI	58.8% (10/17)	89.7% (35/39)	29.4% (5/17)	89.7% (35/39)	Yes	These are the data for reader 2
DeWitt et al. 2004 ³⁶	T staging	MDCT	EUS-FNA	Accurate T stage in 41% (20/49); overstaged T in 14% (7/49), understaged T in 44% (22/49)	See the cell to the left	Accurate T stage in 67% (33/49); overstaged T in 18% (9/49), understaged T in 14% (7/49)	See the cell to the left	Yes	—
Tellez-Avila et al. 2012 ¹⁸	Vessel involvement	MDCT	EUS-FNA	55.6% (10/18)	93.8% (30/32)	61.1% (11/18)	90.6% (29/32)	No	Arteries or veins. Reported cross-classified results in text contained inconsistencies therefore were not extracted
Tellez-Avila et al. 2012 ¹⁸	Vessel involvement	MDCT	EUS-FNA	66.7% (6/9)	90.2% (37/41)	66.7% (6/9)	100% (41/41)	No	Arteries only

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Tellez-Avila et al. 2012 ¹⁸	Vessel involvement	MDCT	EUS-FNA	30% (3/10)	89.7% (35/39)	80% (8/10)	87.5% (35/40)	No	Veins only. Text said 11 positives, but the percentages in Table 3 imply 10 positives
Soriano et al. 2004 ³⁸	T staging	MDCT	MRI	MDCT of 59 patients provided an accurate T stage in 73% (CI 62% to 84%), overstaging in 2% (CI 0%–6%), and understaging in 25% (CI 14%–36%).	See the cell to the left	MRI of 53 patients provided an accurate T stage in 62% (CI 49% to 75%), overstaging in 6% (CI 0%–12%), and understaging in 32% (CI 19%–45%).	See the cell to the left	Yes	Authors did not report how CIS were calculated, but their intervals are similar to those obtained using method 3 of Newcombe et al. 1998. ⁴⁰
Soriano et al. 2004 ³⁸	N staging	MDCT	MRI	37.5% (9/24)	79.4% (27/34)	15% (3/20)	93.3% (28/30)	Yes	Counts determined based on reported information in Table 2 of the article

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Holzapfel et al. 2011 ¹⁹	M staging	MDCT	MRI	53.3% (8/15)	81% (17/21)	86.7% (13/15)	95.5% (42/44)	Yes	Data are per lesion. There were 15 positive metastases in the liver (7 patients), so the denominator for sensitivity was 15 for both tests. However, for specificity, the two tests had different denominators. MDCT specificity data involve a denominator of 21 "no metastasis," whereas MRI specificity data involve a denominator of 44 "benign lesions" (see Tables 1 and 2 of the article).
Motosugi et al. 2011 ²¹	M staging	MDCT	MRI	60% (9/15)	94.9% (37/39)	73.3% (11/15)	94.9% (37/39)	Yes	Reviewer 1 results
Motosugi et al. 2011 ²¹	M staging	MDCT	MRI	60% (9/15)	97.4% (38/39)	86.7% (13/15)	100% (39/39)	Yes	Reviewer 2 results
Motosugi et al. 2011 ²¹	M staging	MDCT	MRI	60% (9/15)	97.4% (38/39)	86.7% (13/15)	100% (39/39)	Yes	Reviewer 3 results
Imai et al. 2010 ²⁵	M staging	MDCT	MRI	0% (0/6)	79.4% (50/63)	0% (0/6)	96.8% (61/63)	Yes	Determination of para aortic lymph node metastasis
Kauhanen et al. 2009 ²⁷	M staging	MDCT	MRI	57.1% (4/7)	85.7% (6/7)	57.1% (4/7)	85.7% (6/7)	Yes	–
Soriano et al. 2004 ³⁸	M staging	MDCT	MRI	54.5% (6/11)	95.8% (46/48)	30% (3/10)	95.3% (41/43)	Yes	Counts determined based on reported information in Table 2 of the article

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Soriano et al. 2004 ³⁸	Precise staging	MDCT	MRI	MDCT of 59 patients provided an accurate TNM stage in 46% (CI 33% to 59%), overstaging in 8% (CI 1%–15%), and understaging in 46% (CI 33%–59%).	See the cell to the left	MRI of 53 patients provided an accurate TNM stage in 36% (CI 23% to 49%), overstaging in 7% (CI 0%–14%), and understaging in 57% (CI 44%–70%).	See the cell to the left	Yes	Authors did not report how CIS were calculated, but their intervals are similar to those obtained using method 3 of Newcombe et al. 1998. ⁴⁰
Koelblinger et al. 2011 ²⁰	Vessel involvement	MDCT	MRI	90% (9/10)	97.5% (119/122)	80% (8/10)	95.9% (117/122)	Yes	These are data for reader 1. Extracted data included those who had surgical reference standard (22 patients, 132 vessels)
Koelblinger et al. 2011 ²⁰	Vessel involvement	MDCT	MRI	70% (7/10)	98.4% (120/122)	50% (5/10)	98.4% (120/122)	Yes	These are data for reader 2. Extracted data included those who had surgical reference standard (22 patients, 132 vessels)
Lee et al. 2010 ²⁶	Vessel involvement	MDCT	MRI	60.7% (17/28)	96.4% (187/194)	57.1% (16/28)	97.9% (190/194)	Yes	These are the data for reader 1. The totals include 222 major vessels assessed during surgery among 47 patients out of 56 patients total

Table C-12. Comparative accuracy data for tests of interest in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Sensitivity	Test 2 Specificity	No Internal Discrepancies in Reported Data?	Comments
Lee et al. 2010 ²⁶	Vessel involvement	MDCT	MRI	64.3% (18/28)	94.3% (183/194)	57.1% (16/28)	99% (192/194)	Yes	These are the data for reader 2. The totals include 222 major vessels assessed during surgery among 47 patients out of 56 patients total
Soriano et al. 2004 ³⁸	Vessel involvement	MDCT	MRI	66.7% (16/24)	94.3% (33/35)	59.1% (13/22)	83.9% (26/31)	Yes	Counts determined based on reported information in Table 2 of the article
Soriano et al. 2004 ³⁸	Resectability after staging	MDCT	MRI	66.7% (18/27)	96.9% (31/32)	56.5% (13/23)	90% (27/30)	Yes	Authors reported data defining unresectable as a negative, but we recorded data with unresectable as a positive. Precise counts not determinable because not all patients received either test (59 received CT and 53 received MRI).
Lemke et al. 2004 ³⁷	N staging	MDCT	PET/CT	25.8% (8/31)	75% (12/16)	32.3% (10/31)	75% (12/16)	No	Only based on those with complete histologic analysis (47 of 104 patients)
Kauhanen et al. 2009 ²⁷	M staging	MDCT	PET/CT	57.1% (4/7)	85.7% (6/7)	85.7% (6/7)	100% (7/7)	Yes	–

Table C-12. Comparable accuracy data for tests of interests in included studies (continued)

Study	Clinical Purpose	Test 1 Name	Test 2 Name	Test 1 Sensitivity	Test 1 Specificity	Test 2 Specifity	Test 2 Sensitivity	No Internal Discrepancies in Reported Data?	Comments
Farma et al. 2008 ²⁸	M staging	MDCT	PET/CT	56.5% (13/23)	91.5% (54/59)	60.9% (14/23)	100% (59/59)	Yes	Counts calculated based on Table 4 of the article
Shami et al. 2011 ²³	Precise staging	EUS-FNA	MRI	EUS-FNA resulted in an accurate stage for 34/48 patients who had undergone surgical exploration.	See the cell to the left	MRI resulted in an accurate stage for 36/48 patients who had undergone surgical exploration.	See the cell to the left	Yes	EUS-FNA understaged 13/48, and overstaged 1/48. Of the 34 correctly staged, 34 were stage 2 and below, and 0 was stage 3 or above. MRI understaged 12/48, and overstaged 0/48. Of the 36 correctly staged, 35 were stage 2 and below, and 1 was stage 3 or above.
Kauhanen et al. 2009 ²⁷	M staging	MRI	PET/CT	57.1% (4/7)	85.7% (6/7)	85.7% (6/7)	100% (7/7)	Yes	

Harms Studies

Table C-13. General information in pancreas-specific studies included for harms data

Study	Country	Names of Clinic(s)	Range of Dates When Patients Received Imaging Tests	Prospective or Retrospective	Funding Source and Disclosed Potential Conflicts of Interest
Bang et al. 2013 ⁴¹	USA	University of Alabama at Birmingham	October 2011 to November 2011	Prospective	One author was a consultant for Boston Scientific Corporation which was the manufacturer for the needles used, however the study compared techniques rather than needles. No statement about conflicts of interest.
Hayashi et al. 2013 ⁴²	Japan	Hokkaido University Hospital	January 2006 to August 2009, or September 2009 to April 2011	Prospective	"The authors do not have any interests to disclose"
Hucl et al. 2013 ⁴³	India	Asian Institute of Gastroenterology	March 2011 to July 2012	Prospective	NR
Iwashita et al. 2013 ⁴⁴	USA	Academic Tertiary Referral Center	May 2011 to December 2011	Retrospective	"K.J. Chang consultant for Olympus Medical Systems Ltd. Japan and Cook Medica; J.G. Lee the speakers bureau of Novartis Pharmaceutical and Cook Medical. All other authors disclosed no financial relationships relevant to this publication."
Katanuma et al. 2013 ⁴⁵	Japan	Center for Gastroenterology, Tiene-Keijinkai Hospital	April 2003 to September 2011	Retrospective	NR
Lee et al. 2013 ⁴⁶	Republic of Korea	Samsung Medical Center	September 2010 to March 2011	Prospective	"This study was supported by the Samsung Medical Center Clinical Research Development Program grant CRS-110-21-1. No other financial relationships relevant to this publication were disclosed."
Lee et al. 2013 ⁴⁷	Republic of Korea	Samsung Medical Center	April 2009 to March 2010	Prospective	"This study was supported by Samsung Medical Center Clinical Research Development Program Grant, # CRS-1-097-32-2."
Ngamruengphong et al. 2013 ⁴⁸	USA	Mayo Clinic in Jacksonville, Florida	January 1996 to January 2012	Retrospective	NR

Table C-13. General information in pancreas-specific studies included for harms data (continued)

Study	Country	Names of Clinic(s)	Range of Dates When Patients Received Imaging Tests	Prospective or Retrospective	Funding Source and Disclosed Potential Conflicts of Interest
Ikezawa et al. 2012 ⁴⁹	Japan	Osaka Medical Center for Cancer and Cardiovascular Diseases	April 2006 to March 2009	Retrospective	"The authors declare that they have no conflicts of interest"
Ootaki et al. 2012 ⁵⁰	USA	Cleveland Clinic	January 2007 to December 2009	Retrospective	Support was provided solely from institutional and/or departmental sources. One doctor is a consultant for Olympus America
Ranney et al. 2012 ⁵¹	USA	Tertiary referral center - University of Alabama at Birmingham	January 2006 to December 2010	Retrospective	One author is a consultant for Boston Scientific and Olympus Medical Systems
Siddiqui et al. 2012 ⁵²	Lebanon	Division of Gastroenterology, American University of Beirut	June 2000 to March 2011	Retrospective	Funded by Thomas Jefferson University Hospital. "The authors attest that they have no commercial associations (e.g. equity ownership or interest, consultancy, patent and licensing agreement, or institutional and corporate association(s) that might be a conflict of interest in relation to the submitted manuscript."
Attila et al. 2011 ⁵³	USA	Oregon Health and Science University	March 1998 to March 2007	Retrospective	NR
Beane et al. 2011 ⁵⁴	USA	Indiana University School of Medicine	January 2002 to May 2009	Retrospective	NR
Choi et al. 2011 ⁵⁵	South Korea	Samsung Medical Center	July 2009 to December 2009	Prospective	NR
Fabbri et al. 2011 ⁵⁶	Italy	Unit of Gastroenterology and Digestive Endoscopy, AUSL Bologna Bellaria-Maggiore Hospital, Bologna, Italy	September 2007 to December 2008	Prospective	NR
Fisher et al. 2011 ⁵⁷	USA	Dartmouth-Hitchcock Medical Center	Since 1998	Retrospective	"The authors did not receive funding for this work"
Iglesias-Garcia et al. 2011 ⁵⁸	Spain	University Hospital of Santiago de Compostela	NR	Retrospective	"Financial support: None." "Potential competing interests: None."
Itoi et al. 2011 ⁵⁹	Japan	Tokyo Medical University	July 2002 to September 2010	Retrospective	NR

Table C-13. General information in pancreas-specific studies included for harms data (continued)

Study	Country	Names of Clinic(s)	Range of Dates When Patients Received Imaging Tests	Prospective or Retrospective	Funding Source and Disclosed Potential Conflicts of Interest
Kopelman et al. 2011 ⁶⁰	Israel	Hillel-Yaffe Medical Centre, Hadera	NR	Prospective	NR
Kubiliun et al. 2011 ⁶¹	USA	University of Miami,	January 2009 through December 2010	Prospective	NR
Reddymasu et al. 2011 ⁶²	USA	Kansas University Medical Center	January 2002 to December 2008	Retrospective	"Conflict of interest: None"
Carrara et al. 2010 ⁶³	Italy	Division of Gastroenterology & Gastrointestinal Endoscopy, Vita-Salute San Raffaele University	2005 to 2008	Retrospective	NR
Kliment et al. 2010 ⁶⁴	Czech Republic	Non-university tertiary referral center, likely CGB Laboratory in Ostrava	January 1 2007 to August 31 2007	Prospective	"The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper."
Song et al. 2010 ⁶⁵	Korea	University of Ulsan College of Medicine, Asan Medical Center,	March 2007 to April 2008	Prospective	NR
Chang et al. 2009 ⁶⁶	South Korea	Asan Medical Center	January 2007 to December 2007	Retrospective	NR
Fisher et al. 2009 ⁶⁷	Australia	Sir Charles Gairdner Hospital	March 2003 to November 2006	Prospective	NR
Hikichi et al. 2009 ^{68,69}	Japan	Fukushima Medical University Hospital	September 2001 to October 2005	Retrospective	NR
Siddiqui et al. 2009 ⁷⁰	USA	Tertiary Referral Centers at Yale University School of Medicine, New Haven, Connecticut and Virginia Piper Cancer Institute, Minneapolis, MN	February 2007 to June 2008	Prospective	NR
Yusuf et al. 2009 ⁷¹	USA	SUNY Downstate Medical Center	February 2001 to June 2007	Retrospective	"Competing interest: None"
Zamboni et al. 2009 ⁷²	Italy	University Hospital Rossi	January 2004 to June 2008	Retrospective	NR
Al-Haddad et al. 2008 ⁷³	USA	Mayo Clinic College of Medicine in Jacksonville FL	March 2005 to March 2006.	Prospective	NR

Table C-13. General information in pancreas-specific studies included for harms data (continued)

Study	Country	Names of Clinic(s)	Range of Dates When Patients Received Imaging Tests	Prospective or Retrospective	Funding Source and Disclosed Potential Conflicts of Interest
Ramirez-Luna et al. 2008 ⁷⁴	Mexico	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.	March 2005 to March 2006.	Retrospective	NR
Shah et al. 2008 ⁷⁵	USA	University of Miami Hospital and Clinics	March 2004 to April 2007	Retrospective	NR
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	USA	University of Alabama at Birmingham	July 2000 to December 2005	Prospective	NR
Rocca et al. 2007 ⁸²	Italy	Molinette Hospital and ASO Ordine Mauriziano	October 2001 to March 2006	Prospective	"Conflict of interest statement: None declared." Partly supported by a grant from Fondazione IBD Inlus
Bournet et al. 2006 ⁸³	France	University affiliated tertiary care referral center	October 2001 to September 2004	Prospective	NR
Mahnke et al. 2006 ⁸⁴	USA	Anschutz Outpatient Pavilion of University of Colorado Hospital's Centers for Advanced Medicine	March 2003 to February 2004	Prospective	Research and Educational grants and honorarium from Olympus American (One Dr.)
Wittmann et al. 2006 ⁸⁵	United Kingdom	University College London Medical School	May 2002 to April 2005	Prospective	NR
Mortensen et al. 2005 ⁸⁶	Denmark	Center for Surgical Ultrasound at Department of Surgical Gastroenterology, Odense University Hospital	December 1991 to December 2002 (complications assessment); 2000 to 2002 (patient tolerability assessment)	Prospective	NR
Ryozawa et al. 2005 ⁸⁷	Japan	Yamaguchi University Hospital and 8 other hospitals in Japan	July 2000 to March 2003	Retrospective	NR
Eloubeidi et al. 2004 ⁸⁸	USA	Multicenter (27 programs of which 19 returned completed datasheet)	Survey of mean 4 years (range 11 months to 9 years) in 19 centers – no dates given (paper published in 2004)	Largely retrospective but had two prospective cohorts in subgroup analysis	NR
Gress et al. 2002 ⁸⁹	USA	Winthrop University Hospital	NR	Prospective	NR

Table C-13. General information in pancreas-specific studies included for harms data (continued)

Study	Country	Names of Clinic(s)	Range of Dates When Patients Received Imaging Tests	Prospective or Retrospective	Funding Source and Disclosed Potential Conflicts of Interest
Harewood et al. 2002 ⁹⁰	USA	Mayo Clinic, Rochester NY and St Vincent's Hospital in Indianapolis IN	1994 to 1999	Prospective	NR
Fritscher-Ravens et al. 2001 ⁹¹	Germany	NR	NR	Prospective	NR
Gress et al. 2001 ⁹²	USA	Indiana University Medical Center	August 1992 to December 1996	Prospective	NR
O'Toole et al. 2001 ⁹³	France	Two centers	January 1998 to October 1999	Retrospective	NR
Voss et al. 2000 ⁹⁴	France	Beaujon Hospital	January 1995 to March 1998	Retrospective	NR
Sakamoto et al. 2008 ⁹⁵	Japan	Kink University	March 2002 to August 2006	Prospective	Supported by the Japan Society for Promotion of Science, Research and Development Committee Program, the Japan Research Foundation for Clinical Pharmacology, and the Japanese Foundation for Research and Promotion of Endoscopy
Agarwal et al. 2004 ³⁵	USA	MD Anderson Cancer Center	November 2000 to November 2001	Retrospective	NR

NR=Not reported

Table C-14. Patient characteristics in pancreas-specific studies included for harms data

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Bang et al. 2013 ⁴¹	Solid noncystic pancreatic lesion referred for EUS-FNA, had not undergone EUS-FNA at other facilities	54	52% (28/54)	63.8 (range 30–88)	36 Pancreatic head/uncinate cancer, 18 pancreatic body/tail cancer	–
Hayashi et al. 2013 ⁴²	Had EUS-FNA, dynamic CT discovered a representative finding of pancreatic ductal adenocarcinoma, no EUS-FNA performed previously	138	55% (76/138)	66.9	112 pancreatic ductal adenocarcinoma, 3 neuroendocrine carcinoma, 2 serous cystic neoplasm, 1 solid pseudopapillary neoplasm, 1 intraductal papillary mucinous adenoma, 1 metastasis from gastric carcinoma, 5 autoimmune pancreatitis, 5 alcoholic chronic pancreatitis, 8 unknown disease	Age was calculated by the EPC based on a weighted average of the age data reported in Table 1 of the article.
Hucl et al. 2013 ⁴³	Consecutive patients eligible for EUS-FNA of pancreatic masses or peri-intestinal lymph nodes of unknown origin	144 (145 lesions)	44% (64/144)	48.4 (18-82)	78 or 139 lesions benign, 38 adenocarcinoma, 9 neuroendocrine tumor, 3 serous cystadenomain, 3 solid pseudopapillary tumor, 1 lymphoma, 1 spinocellular cancer, 14 chronic pancreatitis.	

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Iwashita et al. 2013 ⁴⁴	Consecutive patients undergoing EUS-guided FNAB for solid pancreatic lesions	50	36% (18/50)	Median: 69 (29-90)	35 adenocarcinoma, 6 neuroendocrine tumor, 3 metastatic cancer (hepatocellular carcinoma, renal cell cancer, and melanoma), 1 anaplastic carcinoma, 1 anaplastic large cell lymphoma, 2 autoimmune pancreatitis, 2 nonspecific inflammatory mass, 4 benign	
Katanuma et al. 2013 ⁴⁵	Consecutive patients with pancreatic solid lesions who underwent EUS-FNA procedures	327	45% (149/327)	66.5 (23-92)	275 pancreatic cancer, 24 chronic pancreatitis/tumor forming pancreatitis, 13 pancreatic neuroendocrine tumor, 4 autoimmune pancreatitis, 2 metastatic tumor, 2 solid-pseudopapillary neoplasm, 2 accessory spleen, 5 others	
Lee et al. 2013 ⁴⁶	Patients with solid pancreatic masses, which were diagnosed with CT or magnetic resonance imaging	81	37% (30/81)	59.11	53 pancreatic cancer, 5 metastasis, 4 malignant neuroendocrine tumor, 2 solid-pseudopapillary malignant neoplasm, 1 miscellaneous malignant, 3 chronic pancreatitis, 3 tuberculosis, 2 benign lymphoid tissue, 2 benign neuroendocrine tumor, 2 solid-pseudopapillary malignant neoplasm, 4 benign miscellaneous	

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Lee et al. 2013 ⁴⁷	Patients who were admitted for the evaluation of pancreatic masses diagnosed by transabdominal ultrasonography, computed tomography or magnetic resonance imaging	188 (94 in the 25G needle group and 94 in the 22G needle group)	25G: 44% (42/94) 22G: 42% (40/94)	25G: 61.3 22G: 58.5	104 pancreatic cancer, 13 metastasis, 5 gallbladder and biliary cancer, 4 malignant intraductal papillary mucinous neoplasm, 3 lymphoma, 2 malignant neuroendocrine tumor, 1 malignant gastrointestinal stromal tumor, 17 cyst, 12 serous cystadenoma, 7 benign intraductal papillary mucinous neoplasm, 4 mucinous cystadenoma, 4 benign neuroendocrine tumor, 4 reactive lymph node, 3 pseudocyst, 2 solid pseudopapillary neoplasm, 2 tuberculosis, 1 benign gastrointestinal stromal tumor	
Ngamruengphong et al. 2013 ⁴⁸	All patients who had been diagnosed with malignant solid and cystic neoplasms of the pancreas with potentially resectable tumors and who underwent surgery with curative intent	174	48.9% (85/174)	67	121 Adenocarcinoma, 23 neuroendocrine tumor, 13 mucinous neoplasm, 2 unspecified malignancy, 23 suspicious, 26 negative	
Ikezawa et al. 2012 ⁴⁹	Had pancreatic adenocarcinoma confirmed by histologic and/or cytological findings obtained by either ERCP or EUS-FNA, did not have carcinomatous peritonitis or had follow-up less than 30 days	56	38% (21/56)	64.2	NR	—

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Ootaki et al. 2012 ⁵⁰	Patients who presented with solid pancreatic lesions based on previous imaging studies and patients found to have a pancreatic mass undetected on previous imaging studies were included.	371	48% (177/371)	general Anesthesia group: 63 (SD 14); conscious sedation group: 66 (SD 12)	279 patients successfully diagnosed (specifics not provided), 92 patients had failed diagnoses (specifics not provided)	–
Ranney et al. 2012 ⁵¹	consecutive patients with obstructive jaundice secondary to solid pancreatic mass lesions who underwent EUS-FNA over a 5-year period	214	36% (77/214)	Patients with stents: Median 68 (58–75); Patients no stents: Median 69 (63–78)	Patients with stents: 106 pancreatic cancer, 15 chronic pancreatitis, 22 neuroendocrine or metastatic cancer, 7 indeterminate/atypical. Patients with no stents: 49 pancreatic cancer, 2 chronic pancreatitis, 9 other cancer, 4 indeterminate/atypical	–
Siddiqui et al. 2012 ⁵²	Obstructive jaundice and a solid pancreatic head or uncinate mass found on either 1) transabdominal ultrasound 2) CT or 3) MRI and were in the institution's endoscopy database, and had ERCP whose brush cytology was pathologically interpreted as non-diagnostic or negative for malignancy, and underwent EUS-FNA for diagnosis, and had a biliary stent.	677	49% (332/677)	65.9 (range 41–87)	589 adenocarcinoma, 14 neuroendocrine tumor, 4 lymphoma, 13 metastasis, 57 benign	–

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Attila et al. 2011 ⁵³	Patients 80 years of age or older	232	60% (140/232)	83.8 (SD 1.4, 80–97)	19 AdenoCA, 2 suspicious for malignancy, 1 renal cell carcinoma, 10 negative for malignancy, 1 neuroendocrine, 2 reactive changes, 1 mucinous adenocCA, 1 mucinous neoplasm with dysplastic features	232 represents the entire patient population, but Only 60 patients were evaluated for by EUS-FNA for pancreatic mass lesions. Final diagnoses column represents n=60 for pancreatic mass lesions. Other indications for EUS-FNA evaluation were pancreatic cystic lesions, dilated CBD in the setting of jaundice and/or stricture, evaluation of mediastinal lesions - final diagnoses for these indications are not included in the column.
Beane et al. 2011 ⁵⁴	Underwent EUS-FNA for any indication (210 of 483 were for either pancreatic cyst or pancreatic mass), informed consent, platelet count >50,000/mL, hemoglobin >8 g/dL, international normalized ratio less than or equal to 1.5 28 days prior to EUS-FNA, medically stable to have moderate sedation	483	44% (212/483)	NR	NR	–

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Choi et al. 2011 ⁵⁵	Underwent EUS-FNA for suspected pancreatic malignancy	58	43% (25/58)	59	36 pancreas cancer, 3 malignant IPMN, 2 cholangiocarcinoma, 1 lymphoma, 1 AoV cancer, 1 metastasis, 3 benign serous cystadenoma, 3 benign simple cyst, 2 benign IPMN, 1 benign desmoid tumor, 1 benign GIST, 1 benign inflammation, 1 benign granuloma, 1 benign fibroadipose tissue, 1 benign neuroendocrine tumor	—
Fabbri et al. 2011 ⁵⁶	Diagnosed or suspected solid pancreatobiliary lesions according to clinical evaluation and CT scan.	50	40% (20/50)	68.2 (SD: 7.4 years)	Cytologic diagnosis positive for malignancy found in 40 cases with 25 gauge needle and in 34 cases with 22 gauge needle. Aspirate suspicious for malignancy found in 4 cases with 24 gauge needle and in 6 cases with 22 gauge needle. Final cytologic diagnosis was primary pancreatic adenocarcinoma in 45 (90%) lesions, neuroendocrine in 1 (2%) and 2 inflammatory pseudotumoral masses.	—

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Fisher et al. 2011 ⁵⁷	Age 18+, referred for EUS-FNA at this institution for evaluation of pancreatic head or neck masses, had pancreatic adenocarcinoma, nonadenocarcinomas, no body or tail adenocarcinomas	170	55% (94/170)	68.2	170 pancreatic adenocarcinoma of head or neck	—
Iglesias-Garcia et al. 2011 ⁵⁸	Underwent EUS-FNA of solid pancreatic mass over a two-year period. No EUS-FNAs performed previously	182	40% (73/182)	60.5	115 pancreatic adenocarcinoma, 40 inflammatory mass, 11 neuroendocrine tumor, 8 serous cystadenoma with solid appearance, 4 metastasis, 2 cystadenoma with solid appearance, 1 lymphoma, 1 teratoma	Age is a weighted average based on reported information
Itoi et al. 2011 ⁵⁹	Underwent EUS-FNA and had pancreatic solid mass	356	42% (151/356)	68.2 (range 34–86)	266 pancreatic cancer, 6 endocrine tumor, 7 serous cystadenoma, 3 renal cell carcinoma, 1 lung cancer, 1 solid pseudopapillary neoplasm, 1 shwanoma, 1 malignant lymphoma, 1 desmoid tumor, 54 mass-forming pancreatitis, 15 autoimmune pancreatitis	—
Kopelman et al. 2011 ⁶⁰	Underwent EUS-FNA for suspected pancreatic solid lesion, no coagulopathy	102	40% (41/102)	65	50 adenocarcinoma, 8 neuroendocrine tumors, 8 mucinous tumors, 36 benign pancreatic disease	—

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Kubiliun et al. 2011 ⁶¹	All patients undergoing EUS-FNA for the evaluation of solid pancreatic masses	69	48% (33/69)	65 (38–88)	Pancreatic adenocarcinoma	Started with 206 patients but they only used people with nondiag path for whom FISH was performed)
Reddymasu et al. 2011 ⁶²	Underwent upper abdominal EUS for a pancreas-related indication at this institution, no previous diagnosis of pancreatic cancer, no obvious neoplastic lesion on transabdominal imaging	326	66% (216/326)	57 (range 17–93)	22 pancreatic head adenocarcinoma, 4 pancreatic body adenocarcinoma, 1 pancreatic neck adenocarcinoma, 3 ampullary adenocarcinoma, 3 other pancreaticobiliary malignancy, 56 chronic pancreatitis, 223 benign	–
Carrara et al. 2010 ⁶³	Patients with complications related to EUS-FNA of solid and cystic pancreatic lesions done in the tertiary care university hospital.	1034	NR	NR	NR	–
Kliment et al. 2010 ⁶⁴	Suspected pancreatic cancer diagnoses as a solid mass on CT or MRI or abdominal ultrasound or as a double duct sign on ERCP, and had a solid pancreatic mass detected by EUS. Age ≥18, ability to give informed consent, no high risk for bleeding after EUS-FNA, no large diameter vessel interposed between the needle tip and pancreatic mass.	207	42% (86/207)	62.2 (range 33–89)	155 adenocarcinoma, 4 neuroendocrine tumor, 3 other neoplasia, 1 paraganglioma, 44 benign	–
Song et al. 2010 ⁶⁵	125 consecutive patients with solid pancreatic/peripancreatic mass	115	48% (55/115)	57.68±11.93 years	Adeno, neuroendocrine, cholangio (bile duct), lymphoma, mets, leiomyosarc	–

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Chang et al. 2009 ⁶⁶	Underwent EUS-FNA for pancreatic and peripancreatic lesions, not pancreatic cystic lesion, had adequate follow-up to determine the final nature of the lesion (authors did not define adequacy)	139	46% (64/139)	57 (range 13–85)	88 pancreatic adenocarcinoma, 2 pancreatic neuroendocrine tumor, 8 solid pseudopapillary tumor, 6 pancreatic metastasis, 3 lymphoma, 6 GIST, 1 malignant rhaboid tumor, 2 metastatic stomach cancer or MUO, 1 adrenal metastasis, 1 pheochromocytoma, 1 undifferentiated sarcomatoid cancer	–
Fisher et al. 2009 ⁶⁷	Had EUS-FNA, solid pancreatic lesion(s) (7 patients had 2 lesions, the other 86 had 1 lesion)	93	42% (39/93)	60.6 (range 15–83)	By lesion (N=100): 70 adenocarcinoma, 10 neuroendocrine, 3 lymphoma, 4 other malignancies, 13 benign	–
Hikichi et al. 2009 ^{68,69}	Had EUS-FNA for pancreatic mass and had final diagnoses and had given informed consent	73	33% (24/73)	62	50 ductal adenocarcinoma, 2 malignant endocrine carcinoma, 2 malignant lymphoma, 1 acinar cell carcinoma, 1 carcoma, 1 metastatic tumor, 10 chronic pancreatitis, 5 autoimmune pancreatitis, 1 benign endocrine tumor	Overall age was calculated based on Table 1 of the article.
Siddiqui et al. 2009 ⁷⁰	Suspected pancreatic mass	133	37% (49/133)	70.4	110 adenocarcinoma, 4 neuroendocrine tumor, 1 pseudopapillary tumor, 5 metastatic malignancy, 2 negative, 9 suspicious and/or atypical	

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Yusuf et al. 2009 ⁷¹	Underwent EUS-FNA of pancreatic masses using either 22-gauge or 25-gauge needle at this institution	842	44% (370/842)	66.4	314 adenocarcinoma, 272 negative for malignancy, 79 atypical/inconclusive, 36 blood/nondiagnostic, 23 mucinous neoplasm, 20 Hypocellular/acellular, 30 Neuroendocrine tumor, 14 Chronic pancreatitis, 6 Serous cystadenoma, 45 Other	Age calculated based on weighted average of those receiving 22-gauge or 25-gauge needles
Zamboni et al. 2009 ⁷²	Underwent EUS-FNA of pancreatic masses at this institution, already evaluated by CT or MRI or sonography and patient was referred for biopsy, platelet count at least 50,000/mL, informed consent	545	48% (262/545)	62 (range 25–86)	422 pancreatic adenocarcinoma, 22 neuroendocrine tumor, 18 atypia, 13 pancreatitis, 5 neoplasm undefinable origin, 2 neoplasm with massive necrosis, 4 lymphoma, 2 pseudopapillary tumor, 36 nondiagnostic, 18 normal parenchyma, 1 pseudocyst	–
Al-Haddad et al. 2008 ⁷³	If clinical suspicion of pancreatic cancer was based on: obstructive jaundice with biliary stricture seen on ERCP (n=47), suspected pancreatic mass on CT (n=19), and two or more episodes of acute pancreatitis in 6 months without predisposing factors (n=15)	81	51% (41/81)	66.4 (SD 10.5)	71 malignant and 10 benign	of the 71 malignant tumors: 58 were located in the pancreatic head, five in the uncinate process, and eight in the neck, body or tail of the pancreas)

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Ramirez-Luna et al. 2008 ⁷⁴	patients with clinical, biochemical and/or radiological suspicion (Ultrasound, CT, MRI) of a pancreatic lesion that underwent EUS	53	83% (44/53)	61 (17–87)	Adeno, cystadeno, IPMN, neuroendocrine, NHL, renal mets	–
Shah et al. 2008 ⁷⁵	Patients had a prior imaging study demonstrating a pancreatic mass or clinical and radiological data suggested the presence of a pancreatic tumor; procedures involving solid pancreatic lesions only were selected for this review	72	43% (31/72)	65.9 (SD: 12.3; 27–94)	Pathological diagnosis: 62 (86.1%) malignant pancreatic masses (35 died pancreatic cancer, 17 alive and surgical confirmation, 10 progression of disease); 10 (13.9%) benign pancreatic masses (5 no progression, 5 underwent surgery). Location of Mass: 58 (80.6%) head/uncinate; 14 (19.4%) neck/body/tail	Study compared EUS-FNA to EUS-FNA+TCB; data for this study is only from the EUS-FNA group
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	Had EUS-FNA, suspected pancreatic cancer, informed consent, no abnormal coagulation profile	547	40% (NR)	64	73% pancreatic adenocarcinoma, 7.3% other lesions, 19% pancreatitis, 1% indeterminate	–
Rocca et al. 2007 ⁸²	Received EUS-FNA at one of two units, pathological imaging of pancreas or periampullary region, suspicious for pancreatic cancer	293	47% (138/293)	65.9 (range 58.6–73.6)	193 malignant, 100 benign (other details not reported)	–
Bournet et al. 2006 ⁸³	patients undergoing interventional EUS	224	45% (101/224)	61 (SD 10.7), Range 25–81	NR	–
Mahnke et al. 2006 ⁸⁴	patients undergoing ERCP and/or EUS at the center	160	NR separately for EUS-FNA group	NR separately for EUS-FNA group	NR	Study compared ERCP to EUS with and without FNA; only EUS-FNA data reported.

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Wittmann et al. 2006 ⁸⁵	Underwent EUS-guided tissue sampling, had inconclusive diagnosis after previous percutaneous biopsy OR easier or safer access to the lesion using EUS OR small lesion size precluding percutaneous biopsy, lesions <2 cm only received FNA whereas lesions 2cm+ received both FNA and trucut biopsy	159	45% (71/159)	61	83 pancreas lesions, 55 mediastinum, 9 esophagus, 7 stomach, 2 rectum, 1 hepatic hilum, 1 hypopharynx, 1 duodenum (data were reported specifically for the 83 pancreas lesions)	–
Mortensen et al. 2005 ⁸⁶	All patients who had undergone EUS and registered Prospectively	670	NR separately for EUS-FNA group	NR	369 of 670 malignant; 301 benign	EUS-FNA was performed in 670 of 3324 EUS assessments
Ryozawa et al. 2005 ⁸⁷	Pancreatic lesions or parapancreatic disease and underwent EUS-FNA one of the study institutions	52	29% (15/52)	62.5 (range 33–85)	29 pancreatic ductal adenocarcinoma, 2 acinar cell carcinoma, 1 bile duct cancer, 8 chronic pancreatitis, 10 benign pancreatic cyst, 2 pancreatic abscess	–
Eloubeidi et al. 2004 ⁸⁸	List of centers in the US that offer training in EUS contacted by email to EUS program director with invitation to participate. Requested information included total number EUS-FNAs of solid pancreatic masses performed, duration of time over which these procedures were performed and whether any case of acute pancreatitis.	27 programs contacted – 19 programs (70%) returned completed data sheet	NA	NA	Patient specific information not provided – rather self-reported episode of acute pancreatitis at EUS training centers with measure of severity.	–

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Gress et al. 2002 ⁸⁹	Referred for EUS-FNA at this institution, provided informed consent	100	44% (44/100)	64.2	83 pancreas head mass, 14 pancreas body mass, 3 pancreas tail mass	Mean age calculated based on a weighted average of men's and women's average age
Harewood et al. 2002 ⁹⁰	Known or suspected solid pancreatic mass, seen at one of two institutions, informed consent, biopsy requested by referring physician	185	34% (63/185)	65.2	155 adenocarcinoma, 7 neuroendocrine, 2 lymphoma, 20 chronic pancreatitis, 1 lipoma	–
Fritscher-Ravens et al. 2001 ⁹¹	Patients with focal pancreatic masses detected on CT	114	NR	NR	112 patients with adequate material obtained from EUS-FNA: 65 primary pancreatic malignancy, 12 metastatic tumor, 35 benign lesion	–
Gress et al. 2001 ⁹²	Referred for further evaluation of suspected pancreatic cancer, had negative ERCP sampling and subsequently underwent CT-guided biopsy, patients with negative results on CT-guided biopsy who subsequently underwent ERCP with sampling, patients with negative results on CT-guided biopsy who did not have sampling at ERCP	102	43% (44/102)	Mean 63.6, Median 65	61 pancreatic cancer, 41 no pancreatic cancer	–
O'Toole et al. 2001 ⁹³	Patients with suspected lesions involving or adjacent to upper or lower GI tract	322	47% (151/322)	59.5	NR	248/322 had pancreas investigation; data specific to pancreatic.

Table C-14. Patient characteristics in pancreas-specific studies included for harms data (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Specific Final Diagnoses	Comments
Voss et al. 2000 ⁹⁴	Underwent EUS-FNA for the diagnosis of solid pancreatic mass at this institution, did not have easily accessible metastases that could be biopsied more easily, not a purely cystic tumor or pseudocyst	99	NR	NR	59 pancreatic adenocarcinoma, 15 neuroendocrine tumor, 5 IPMN, 1 cystic and papillary tumor, 10 pancreatitis	–
Sakamoto et al. 2008 ⁹⁵	Suspected of having a pancreatic solid tumor due to abnormal screening findings on EUS or CT, informed consent	119	39% (47/119)	68.7	119 pancreatic carcinoma, 16 inflammatory pseudotumors, 19 endocrine tumors, 2 metastatic pancreatic tumor from renal cell carcinoma	Patient characteristics not reported specifically for the 98/156 who received EUS-FNA. Reported characteristics are for the 119/156 patients who had pancreatic ductal carcinoma.
Agarwal et al. 2004 ³⁵	Primary pancreatic neoplasm and underwent distal pancreatectomy, no previous pancreatic resection, no metastatic neoplasm, represented in the institution's database	179	64% (114/179)	61 (range 19–86)	57 adenocarcinoma, 42 cystic neoplasm, 14 serous, 28 mucinous, 33 IPMN, 34 endocrine neoplasm	The N of 179 includes only those who received EUS and FNA.

CT=Computed tomography; ERCP=endoscopic retrograde cholangiopancreatography; EUS=endoscopic ultrasound; EUS-FNA=Endoscopic ultrasound - fine needle aspiration; FISH=fluorescence in situ hybridization; GI=gastrointestinal; GIST=gastrointestinal stromal tumor; IPMN=intraductal papillary mucinous neoplasm; mL=milliliter; MRI=magnetic resonance imaging; NR=not reported; SD=standard deviation

Table C-15. Testing characteristics in pancreas-specific studies included for harms data

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Bang et al. 2013 ⁴¹	EUS-FNA	Device: Olympus UCT140 Needle Type: Expect needle, Needle Size: 22G or 25G	25G via transduodenal route for head/uncinate lesions. 22G via transgastric route for body/tail lesions	54/54	1	NR	NR

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Hayashi et al. 2013 ⁴²	EUS-FNA	Device: GF-UCT240P-AL5 (Olympus) Needle Type: Echotip Needle Size: 22G	NR	138/138	2	NR	Endosonographers underwent extensive training for review of cytological smear alongside a pathologist (T.H.) during routine EUS-FNA for pancreatic lesion in period 1. Endosonographers were taught to identify normal pancreatic cells (ductal epithelium, acinar cell, and islet cell) in direct smear to easily detect atypical epithelial cells within abundant cell clusters.
Hucl et al. 2013 ⁴³	EUS-FNA	Device: GF-UCT 180 with EU-ME1 processor (Olympus) Needle Type: EchoTip and EchoTip ProCore Needle Size: 22G FNA and 22G Core FNB	EchoTip ProCore made of stainless steel, 8cm long with a sheath size of 5.2 Fr and incorporates a reverse bevel technology	145/145	3 pathologists (1 of 3 evaluated each sample)	Pathologists had an interest in pancreatic pathology.	Examinations and biopsies were performed by 2 experienced endoscopists
Iwashita et al. 2013 ⁴⁴	EUS-FNA	Device: GF-UC140P-AL5 (Olympus) Needle Type: NR Needle Size: 25G	Patients were under moderate sedation or general anesthesia	50/50	1	Pathologist	---

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Katanuma et al. 2013 ⁴⁵	EUS-FNA	Device: GF-UCT240 or GF-UCT260 (Olympus) Needle Type: EZ-shot (Olympus) or EchoTip (Cook Medical) Needle Size: 10G or 22G	All patients were placed in the left lateral position	327/327	NR	NR	"Procedures were performed by physicians who perform an average of 150 patients per year and have more than 10 years experience."
Lee et al. 2013 ⁴⁶	EUS-FNA	Device: NR Needle Type: Endocoil or EchoTip (Cook Medical) Needle Size: 22G or 25G	"The choice of a needle was made of an operator's own will to achieve the safest and most successful puncturing. Four punctures were performed for each mass in random order (computer generated)."	81/81	1	"experienced cytopathologist"	"Cytopathologist was blinded to the use of suction during puncturing and the expression techniques"
Lee et al. 2013 ⁴⁷	EUS-FNA	Device: GF-UM30 or GF-UCT240P-AL5 (Olympus) Needle Type: Endocoil (Wilson-Cook) or EchoTip (Wilson-Cook) Needle Size: 22G or 25G	"Transgastric approach was tried initially for a mass of the body or tail and transduodenal approach for that of the head or ucinat process."	188 (94/188 22G and 94/188 25G)	1 cytopathologist	NR	"Endosonographers at hospital are highly experienced for this procedure (more than 500 cases of EUS-FNA per year)."

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Ngamruengphong et al. 2013 ⁴⁸	EUS-FNA	Device: GF-UCTP 140 (Olympus) Needle Type: NR Needle Size: 19G, 22G, or 25G	NR	174/174	NR	NR	3 endosonographers conducted EUS-FNA. Endoscopist 1 performed 71 procedures, Endoscopist 2 performed 43, Endoscopist 3 performed 73, and outside endoscopists performed 21.
Ikezawa et al. 2012 ⁴⁹	EUS-FNA	Device: UCT2000 (Olympus) Needle Type: Echotip Needle Size: 22G or 25G	Transgastric approach in 26 patients, transduodenal in 29 patients, and small intestine after total gastrectomy in 1 patient	56/56	2	NR	NR
Ootaki et al. 2012 ⁵⁰	EUS-FNA	NR	NR	371/371	NR	NR	NR
Ranney et al. 2012 ⁵¹	EUS-FNA	Device: UCT 140 (Olympus) Needle Type: Echotip Needle Size: 22G or 25G	NR	214/214	1	NR	NR
Siddiqui et al. 2012 ⁵²	EUS-FNA	Device: GF UCT 140 (Olympus) or UCT 160 (Olympus) Needle Type: Echotip Needle Size: 22G	Transduodenal approach	677/677	NR	Experienced faculty endoscopists who had performed greater than 500 EUS procedures	NR

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Attila et al. 2011 ⁵³	EUS-FNA	Device: GF-UC140P AL5 (Olympus) and GF-UM160 (Olympus) or FG36UX (Pentax) Needle Type: Wilson Cook Needle Size: 19G or 22G	NR	95/95	NR	NR	NR
Beane et al. 2011 ⁵⁴	EUS-FNA	Device: GF-UC140P (Olympus) Needle Type: Echotip Ultra Needle Size: 19G, 22G, or 25G	NR	179/179	6 gastroenterologists	Extensive experience with pancreatic EUS	The number of passes per site, needle gauge, use of a stylet, and suction were left to the discretion of the endosonographer. Any procedure-related complications occurring after EUS-guided FNA were recorded independently.
Choi et al. 2011 ⁵⁵	EUS-FNA	Device: GF-UCT240P-AL5 (Olympus) Needle Type: Endocoil or Echotip Needle Size: 22G or 25G	NR	58/58	NR	NR	NR

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Fabbri et al. 2011 ⁵⁶	EUS-FNA	Device: NR Needle Type: EchoTip Ultra with HDFNA (Cook Endoscopy) Needle Size: 19G, 22G, or 25G	140 cm long stainless steel needle within a spiral steel sheath surrounded by a Teflon cover. Prospective comparative study with randomization of needle sequence.	50/50	3	1 Endoscopist with current case volume of 700 cases per year. 2 on-site pathologists experienced in gastrointestinal cytology	NR
Fisher et al. 2011 ⁵⁷	EUS-FNA	Device: Olympus linear echoendoscopes Needle Type: Echotip, Olympus Needle (not specified), or unknown needle Size: 22G or 25G	Echotip for 42%, Olympus for 24%, combination for 9%, unknown for 23% 22G for 54%, 25G for 35%, combination needle for 11%, unknown for 0.6%	170/170	NR	Expert endosonographers	NR
Iglesias-Garcia et al. 2011 ⁵⁸	EUS-FNA	Device: EG-3870UTK (Pentax) Needle Type: Wilson-Cook (name not specified) Needle Size: 22G	Transduodenal approach for pancreatic head lesions, or transgastric approach for body/tail lesions	182/182	2	NR	NR

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Itoi et al. 2011 ⁵⁹	EUS-FNA	Device: GF UCT 2000 (Olympus) or UCT 240 (Olympus) Needle Type: Echotip and Echotip Ultra aspiration needles or trucut needles (Quickcore) Needle Size: 19G, 22G, or 25G	The trucut needles were reserved for body/tail masses.	356/356	NR	NR	NR
Kopelman et al. 2011 ⁶⁰	EUS-FNA	Device: 5 MHz frequency 36UX - FG EUS (Pentax) Needle Type: Wilson Cook Medical (name not specified) Needle Size 22G	Transduodenal approach for pancreatic head lesions, or transgastric approach for body/tail lesions	102/102	1	Experienced examiner	NR
Kubiliun et al. 2011 ⁶¹	EUS-FNA	Device: UC-30P or UCT 140 (Olympus) Needle Type: EchoTip (Cook Endoscopy) Needle Size: 22G	On-site cytopathologist. If on-site read was non-diagnostic then patients referred for FISH which was the test of interest	69/69	1	NR	Endoscopist performed all EUS-FNA procedures
Reddymasu et al. 2011 ⁶²	EUS-FNA	Device: EG-3630UR (Pentax) Needle Type: NR Needle Size: NR	NR	326/NR	2	Mojtaba Olyaei, MD performs approximately 800 procedures per year and Syed Jafri, MD performs approximately 500 EUS examinations per year.	NR

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Carrara et al. 2010 ⁶³	EUS-FNA	Device: FG36UX (Pentax) or EG3830UT (Pentax) Needle Type: Wilson Cook (name not specified) Needle Size: 22G or 25G	NR	1,034/1,034	1	NR	NR
Kliment et al. 2010 ⁶⁴	EUS-FNA	Device: GF-UC140 (Olympus) Needle Type: AL EZ-Shot Needle Size: 22G	NR	207/207	2	Experienced	Depending on the echoendoscopist's decision, when clinically relevant, EUS-FNA of ascitic fluid, suspicious lymph node, liver mass or other site was performed before sampling pancreatic mass. number of needle passes depended on the echoendoscopist's decision
Song et al. 2010 ⁶⁵	EUS-FNA	Device: GF-UCT 240 (Olympus) Needle Type: ECHO 3-22 or ECHO 19 (Cook Endoscopy) Needle Size: 19G or 22G	NR	117/177	NR	NR	NR

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Chang et al. 2009 ⁶⁶	EUS-FNA	Device: GF-UM 2000 (Olympus) or GF-UCT 240 (Olympus) Needle Type: Echotip-22ECHO or Echotip-ECHO 19 or trucut needle quick-core Needle Size: 19G or 22G	NR	139/139	2	Experienced endosonographers	Needle type used determined by the operator at will
Fisher et al. 2009 ⁶⁷	EUS-FNA	Device: UC-140P (Olympus) Needle Type: Wilson-Cook (name not specified) Needle Size: 22G	Trangastric approach for 27 body/tail lesions, and transduodenal for the 73 head lesions	93/93	2	Gastroenterologist or supervised EUS fellow.	NR
Hikichi et al. 2009 ^{68,69}	EUS-FNA	Device: GF-UCT240-AL5 (Olympus) or GF-U240P-AL5 (Olympus), FG-36UX (Pentax), or EUB-6000 (Hitachi) Needle Type: Echotip or NA-10J-I (Olympus) or NA-200H-8022 (Olympus) Needle Size: 22G	—	73/73	10	A.I. had 13 years' experience with EUS at the beginning of period 1, and T.H. had 7 years' experience with EUS at the beginning of period 1. The other eight operators were trainees with at least 5 years' experience of EUS at beginning of period 1 or 2.	When the endosonographers or cytopathologist indicated the amounts of cell samples were adequate, the procedure was stopped.

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Siddiqui et al. 2009 ⁷⁰	EUS-FNA	Device: GF-UCT 140 series (Olympus) Needle Type: Endocoil or Echotip (Wilson Cook) Needle Size: 22G or 25G	22 gauge: mean needle passes 2.6 (SD 1.2), needle malfunction in 11 patients. 25 gauge: mean needle passes 2.6 (1.2), needle malfunction in 10 patients	133/133	NR	NR	NR
Yusuf et al. 2009 ⁷¹	EUS-FNA	Device: GF-UM20 (Olympus), FG36UX (Pentax), FG38UX (Pentax) Needle Type: Echotip Needle Size: 22G or 25G	NR	842/842	NR	Experienced endosonographers trained in radial and linear array endosonography and EUS-guided FNA.	NR
Zamboni et al. 2009 ⁷²	EUS-FNA	Device: Sequoia 512 6.0 Needle Type: Menghini Needle Size: 20G or 21G	Anterior abdominal approach for all cases	545 / 545	NR	All biopsies were performed in our department on an inpatient basis by members of our interventional ultrasound team.	NR

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Al-Haddad et al. 2008 ⁷³	EUS-FNA	Device: UC30P (Olympus), UCT140 (Olympus), GFUM-130 (Olympus), or GF-UE-160 (Olympus) Needle Type: Echotip (Wilson-Cook) Needle Size 19G, 22G, or 25G	NR	210 / 210	3	Attending endosonographers performed all the procedures and were assisted by fellows in over 90% of cases. Two of the three attending endosonographers underwent third-tier EUS training and had all previously performed more than 1,000 procedures independently.	NR
Ramirez-Luna et al. 2008 ⁷⁴	EUS-FNA	Device: GF UCT-140 (Olympus) Needle Type: ECHO TIP (Wilson-Cook) Needle Size: 19G or 22G	NR	52 / 52	1	"Experienced"	Endoscopist performed all EUS-FNA procedures
Shah et al. 2008 ⁷⁵	EUS-FNA	Device: GF-UC140P (Olympus) and GF-UCT140 (Olympus) with Aloka processor Needle Type: Echotip (Wilson-Cook) Needle Size: 22G	10 mL suction	72/72	2	"Experienced"	NR

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	EUS-FNA Olympus UC-30P or UC 140T Echotip 22 gauge	EUS-FNA Olympus UC-30P or UC 140T Echotip 22 gauge	547/547	1	NR	Any symptoms reported by the patient during recovery time were carefully assessed and documented by the endoscopist.
Rocca et al. 2007 ⁸²	EUS-FNA	Device: GF-UCP140 (Olympus), 38UX (Pentax), or 36UX Needle Type: ECHO-3-22 Needle Size: 22G	NR	293/232	NR	NR	NR
Bournet et al. 2006 ⁸³	EUS-FNA	Device: GF-UC30P (Olympus) or FG36UX (Pentax) Needle Type: EUS-N1 (Wilson Cook) Needle Size: 22G or 19G	maximum of 3 to 4 needle passes generally done, only one needle pass for cystic tumors, mean time for procedure 24.7 minutes (SD 5)	224/224	NR	NR	NR
Mahnke et al. 2006 ⁸⁴	EUS-FNA	NR	NR	160/160	NR	NR	NR
Wittmann et al. 2006 ⁸⁵	EUS-FNA	Device: GIF UC 30P (Olympus) or 38UX (Pentax) Needle Type: Echotip Needle Size: 22G	NR	83/83	1	Experienced	Usually a day-case procedure
Mortensen et al. 2005 ⁸⁶	EUS-FNA	NR	NR	670 of 3,324/ 670 of 3,324	NR	NR	NR

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Ryozawa et al. 2005 ⁸⁷	EUS-FNA	Device: GIF UC30P (Olympus) or GF-UC2000P-OL5 (Olympus) Needle Type: NA10J-1 or NA-11J-KB or Echotip Needle Size: NR	NR	52/52	1	One well-trained endoscopist (S.R.) performed EUS-FNA in all patients.	NR
Eloubeidi et al. 2004 ⁸⁸	EUS-FNA	Device: NR Needle Type: NR Needle Size: NR	NR	NA – 19 of 27 training programs responded to questionnaire. List of centers in which training in EUS is offered obtained from Web site of the American Society for Gastrointestinal Endoscopy	NR	NR	NR
Gress et al. 2002 ⁸⁹	EUS-FNA	Device: EUM-20 (Olympus) and FG32UA GIP (Pentax) Needle Type: Mediglobe Needle Size: 22G	Transduodenal approach for pancreatic head lesions, or transgastric approach for body/tail lesions	100/100	2	Experienced	NR

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Harewood et al. 2002 ⁹⁰	EUS-FNA	Device: GF-UM20 (Olympus), GF-UM30 (Olympus), GF-UC30P (Olympus), or FG-32UA (Pentax) Needle Type: Wilson-Cook (name not specified) Needle Size: 22G	Transduodenal approach for pancreatic head lesions, or transgastric approach for body/tail lesions	185/185	1	Experienced	NR
Fritscher-Ravens et al. 2001 ⁹¹	EUS-FNA	Device: FG-34UX (Pentax) or GIF-UC30P (Olympus) Needle Type: Wilson-Cook (name not specified) Needle Size: 22G	All procedures performed by a single examiner who received additional training in preparing aspirated material and assessing cellular adequacy.	114 (112 had adequate sampling)/ 114 (112 had adequate sampling)	1	Experienced cytopathologist	Was not present during the EUS procedure and was blinded to the details of the cases
Gress et al. 2001 ⁹²	EUS-FNA	Device: EUM-20 (Olympus) or FG32UA (Pentax) Needle Type: Wilson Cook or GID/Mediglobe Needle Size: 23G 4 cm (Wilson) or 22G 10 cm (GID/Mediglobe)	Median number of passes of biopsy was 3.4 (range 2 to 9)	102/102	1	Particular competence in pathologic-anatomical diagnosis	Pathologist

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
O'Toole et al. 2001 ⁹³	EUS-FNA	Device: GF-UM20 (Olympus), FG-32UA (Pentax) Needle Type: Hancke-Vilman GIP (Pentax) or Hexa Medical or NA-10J-1 (Olympus) Needle Size: 22G 12 cm (Hancke-Vilman GIP or Hexa Medical) or 22G 6 cm (Olympus)	Mean number of passes 2.1 per lesion (SD 1.0). Procedure performed in 2 centers by 3 experienced endosonographers	322/322	NR	NR	NR
Voss et al. 2000 ⁹⁴	EUS-FNA	Device: FG 32 UA (Pentax) 120 degree Needle Type: NR Needle Size: 22G	Transduodenal approach for pancreatic head lesions, or transgastric approach for body/tail lesions	99/90	NR	NR	NR
Sakamoto et al. 2008 ⁹⁵	MDCT, EUS-FNA	MDCT Device: Toshiba Aquillion (Toshiba medical systems) MDCT Slice Thickness: 5mm MDCT Reformats: NR MDCT Contrast: 100 mL Optiray 320 MDCT Phases of Enhancement: NR EUS-FNA Device: GF-UCT240-AL5 (Olympus) Needle Type: Echotip Needle Size: 22G	NR	156/98	2	Qualified by the Japan Gastroenterological Endoscopy Society	To prevent inter-operator variability, all procedures were performed by the same operators using the same examination protocol

Table C-15. Testing characteristics in pancreas-specific studies included for harms data (continued)

Study	Test	Test Technology	Additional Test Details	Number of Patients in Study Received Test/ Number of Patients Received EUS-FNA	Number of Test Readers	Reader Prior Experience	Additional Reader Details
Agarwal et al. 2004 ³⁵	MDCT vs. EUS-FNA	MDCT Device: NR MDCT Slice Thickness: 1.25 mm (parenchymal phase), 2.5 mm (portal phase) MDCT Reformats: NR MDCT Contrast: 150 mL Optiray 320 (Mallinckrodt Inc.) MDCT Phases of Enhancement: Dynamic EUS-FNA Device: EUM-30 (Olympus) and FG-32A (Olympus) Needle Type: Echo-tip (Wilson Cook) Needle Size: NR	EUS-FNA was considered positive only if a definitive cytologic diagnosis of malignancy could be made with fine needle aspirates.	81/81	NR	NR	CT: radiologists who specialize in body imaging. EUS-FNA: Cytologist could make the preliminary diagnosis

EUS=Endoscopic ultrasound; EUS-FNA=endoscopic ultrasound-fine needle aspiration; G=gauge; MDCT=multi-detector computed tomography; mm=millimeter; MRI=magnetic resonance imaging; NR=not reported

Table C-16. Harms reported in included pancreas-specific studies

Study	Test	Harm	Rate	Number of Patients at Risk of Harm	Number of Patients Experienced Harm	Comments
Bang et al. 2013 ⁴¹	EUS-FNA	Any	0% (0/54)	54	0	—
Hayashi et al. 2013 ⁴²	EUS-FNA	Punctures resulting in peripancreatic abscess and requiring antibiotics	0.7% (1/138)	138	1	—
Hucl et al. 2013 ⁴³	EUS-FNA	Any	0% (0/145)	145	0	--
Iwashita et al. 2013 ⁴⁴	EUS-FNA	Any	0% (0/50)	50	0	--
Katanuma et al. 2013 ⁴⁵	EUS-FNA	Moderate Pancreatitis	0.3% (1/327)	327	1	--
Katanuma et al. 2013 ⁴⁵	EUS-FNA	Mild Pancreatitis	1.5% (5/327)	327	5	--
Katanuma et al. 2013 ⁴⁵	EUS-FNA	Mild Abdominal Pain	1.2% (4/327)	327	4	--
Katanuma et al. 2013 ⁴⁵	EUS-FNA	Mild Bleeding	0.3% (1/327)	327	1	--
Lee et al. 2013 ⁴⁶	EUS-FNA	Mild Acute Pancreatitis	2.4% (2/81)	81	2	--
Lee et al. 2013 ⁴⁷	EUS-FNA	Pancreatitis	3.7% (7/188)	188	7	25G group (1) and 22G group (6)
Lee et al. 2013 ⁴⁷	EUS-FNA	Bleeding	3.2% (6/188)	188	6	25G group (2) and 22G group (4)
Lee et al. 2013 ⁴⁷	EUS-FNA	Infection	0% (0/188)	188	0	--
Lee et al. 2013 ⁴⁷	EUS-FNA	Perforation	0% (0/188)	188	0	--
Ngamruengphong et al. 2013 ⁴⁸	EUS-FNA	Tumor Seeding	0% (0/174)	174	0	--
Ikezawa et al. 2012 ⁴⁹	EUS-FNA	Mild pancreatitis treated conservatively	1.8% (1/56)	56	1	—
Ikezawa et al. 2012 ⁴⁹	EUS-FNA	EUS-FNA-induced peritoneal carcinomatous peritonitis	17.9% (10/56)	56	10	Average length of follow-up 599 days
Ootaki et al. 2012 ⁵⁰	EUS-FNA	Self-limited bleeding during or after EUS-FNA (in conscious sedation group)	0.5% (2/371)	371	2	—

Table C-16. Harms reported in included pancreas-specific studies (continued)

Study	Test	Harm	Rate	Number of Patients at Risk of Harm	Number of Patients Experienced Harm	Comments
Ranney et al. 2012 ⁵¹	EUS-FNA	Any	0% (0/214)	214	0	–
Siddiqui et al. 2012 ⁵²	EUS-FNA	Bowel perforations	0% (0/677)	677	0	–
Siddiqui et al. 2012 ⁵²	EUS-FNA	Significant intra-procedural bleeding after FNA	0% (0/677)	677	0	–
Siddiqui et al. 2012 ⁵²	EUS-FNA	Mild acute pancreatitis (resolved within one day)	0.3% (2/677)	677	2	–
Siddiqui et al. 2012 ⁵²	EUS-FNA	Abdominal pain	0.1% (1/677)	677	1	One day after the procedure
Attila et al. 2011 ⁵³	EUS-FNA	Any	0% (0/95)	95	0	95 of 232 had EUS-FNA
Choi et al. 2011 ⁵⁵	EUS-FNA	Any significant procedure-related complications such as bleeding or pancreatitis	0% (0/58)	58	0	–
Beane et al. 2011 ⁵⁴	EUS-FNA	Acute pancreatitis requiring hospital admission and conservative treatment	1.1% (2/179)	179	2	Post procedural
Beane et al. 2011 ⁵⁴	EUS-FNA	Brief hypoxia requiring temporary airway support	0.6% (1/179)	179	1	Intraoperative
Beane et al. 2011 ⁵⁴	EUS-FNA	Overall morbidity	39.7% (71/179)	179	71	Post procedural. Morbidities included pancreatic fistulas, or surgical site infections, or hemorrhage, or drainage required.
Beane et al. 2011 ⁵⁴	EUS-FNA	Surgical site infection	6.7% (12/179)	179	12	Post procedural
Beane et al. 2011 ⁵⁴	EUS-FNA	Pancreatic fistula	15.1% (27/179)	179	27	Post procedural
Beane et al. 2011 ⁵⁴	EUS-FNA	Drainage procedures	3.4% (6/179)	179	6	Post procedural
Fabbri et al. 2011 ⁵⁶	EUS-FNA	ANY	0% (0/50)	50	0	–
Fisher et al. 2011 ⁵⁷	EUS-FNA	Pancreatitis	2.4% (4/170)	170	4	–

Table C-16. Harms reported in included pancreas-specific studies (continued)

Study	Test	Harm	Rate	Number of Patients at Risk of Harm	Number of Patients Experienced Harm	Comments
Fisher et al. 2011 ⁵⁷	EUS-FNA	Bleeding (self-limited)	0% (0/170)	170	0	—
Fisher et al. 2011 ⁵⁷	EUS-FNA	Perforation	0.6% (1/170)	170	1	—
Fisher et al. 2011 ⁵⁷	EUS-FNA	Bile leak	0.6% (1/170)	170	1	—
Iglesias-Garcia et al. 2011 ⁵⁸	EUS-FNA	Mild acute pancreatitis, requiring hospitalization for 4–5 days	1.1% (2/182)	182	2	—
Iglesias-Garcia et al. 2011 ⁵⁸	EUS-FNA	Bleeding at site of gastric puncture	0.5% (1/182)	182	1	—
Iglesias-Garcia et al. 2011 ⁵⁸	EUS-FNA	Mortality due to the procedure	0% (0/182)	182	0	—
Itoi et al. 2011 ⁵⁹	EUS-FNA	Procedure-related bleeding, treated by conservative therapy without blood transfusion	0.6% (2/356)	356	2	—
Itoi et al. 2011 ⁵⁹	EUS-FNA	Any morbidity other than procedure-related bleeding	0% (0/356)	356	0	—
Kubiliun et al. 2011 ⁶¹	EUS FNA	Any	0% (0/69)	69	0	Nurse called patients 24–48 hours after the procedure
Kopelman et al. 2011 ⁶⁰	EUS-FNA	Any morbidity other than mild pancreatitis	0% (0/102)	102	0	—
Kopelman et al. 2011 ⁶⁰	EUS-FNA	Mild pancreatitis resolved spontaneously	1% (1/102)	102	1	—
Reddymasu et al. 2011 ⁶²	EUS-FNA	Any	0% (0/326)	326	0	—
Kliment et al. 2010 ⁶⁴	EUS-FNA	Any major complications	0% (0/207)	207	0	—
Kliment et al. 2010 ⁶⁴	EUS-FNA	Minor pain treated with a single dose of analgesics	1% (2/207)	207	2	—
Kliment et al. 2010 ⁶⁴	EUS-FNA	Minor bleeding without treatment necessary	1.4% (3/207)	207	3	—
Carrara et al. 2010 ⁶³	EUS-FNA	Mild intracystic hemorrhage	0.6% (6/1034)	1034	6	Indications for EUS-FNA: 3 IPMNs, 1 Chronic Pancreatitis, 1 Cysto- adeno, 1 Cystic adenoCA

Table C-16. Harms reported in included pancreas-specific studies (continued)

Study	Test	Harm	Rate	Number of Patients at Risk of Harm	Number of Patients Experienced Harm	Comments
Carrara et al. 2010 ⁶³	EUS-FNA	Mild intracystic and retroperitoneal hemorrhage	0.1% (1/1034)	1034	1	Indication for EUS-FNA was IPMN
Carrara et al. 2010 ⁶³	EUS-FNA	Mild endoductal hemorrhage	0.2% (2/1034)	1034	2	Indications for EUS-FNA: 1 AdenoCA, 1 Chronic Pancreatitis
Carrara et al. 2010 ⁶³	EUS-FNA	Mild hemorrhage	0.1% (1/1034)	1034	1	Indication for EUS-FNA was AdenoCA
Carrara et al. 2010 ⁶³	EUS-FNA	Moderate acute pancreatitis	0.1% (1/1034)	1034	1	Indication for EUS-FNA was NET
Carrara et al. 2010 ⁶³	EUS-FNA	Severe acute pancreatitis	0.1% (1/1034)	1034	1	Indication for EUS-FNA was acute pancreatitis
Carrara et al. 2010 ⁶³	EUS-FNA	Severe perforation/death	0.1% (1/1034)	1034	1	Indication for EUS-FNA was neuroendocrine tumor
Song et al. 2010 ⁶⁵	EUS FNA	Elevated pancreas enzyme without abdominal pain (chem pancreatitis)	2.6% (3/117)	117	3	Don't specify what time interval they followed patients out to for complications
Chang et al. 2009 ⁶⁶	EUS-FNA	Threefold increase in serum amylase	7.9% (11/139)	139	11	—
Chang et al. 2009 ⁶⁶	EUS-FNA	"Clinical" pancreatitis (did not define "clinical")	0% (0/139)	139	0	—
Fisher et al. 2009 ⁶⁷	EUS-FNA	Minor mucosal bleeding requiring adrenaline injection	1.1% (1/93)	93	1	—
Fisher et al. 2009 ⁶⁷	EUS-FNA	Pain requiring hospital re-admission	1.1% (1/93)	93	1	—
Fisher et al. 2009 ⁶⁷	EUS-FNA	Mild self-limiting mucosal bleeding, stopped without intervention	4.3% (4/93)	93	4	Intraprocedural
Fisher et al. 2009 ⁶⁷	EUS-FNA	Puncture of the superior mesenteric vein	1.1% (1/93)	93	1	—
Fisher et al. 2009 ⁶⁷	EUS-FNA	Perforation	0% (0/93)	93	0	—
Fisher et al. 2009 ⁶⁷	EUS-FNA	Pancreatitis	0% (0/93)	93	0	—
Fisher et al. 2009 ⁶⁷	EUS-FNA	Sepsis	0% (0/93)	93	0	—
Hikichi et al. 2009 ^{68,69}	EUS-FNA	Any major complications	0% (0/73)	73	0	—

Table C-16. Harms reported in included pancreas-specific studies (continued)

Study	Test	Harm	Rate	Number of Patients at Risk of Harm	Number of Patients Experienced Harm	Comments
Hikichi et al. 2009 ^{68,69}	EUS-FNA	Pancreatitis	0% (0/53)	53	0	The lack of pancreatitis was reported by the secondary publication ⁶⁹ which had enrolled 53 patients between 1/2001 and 12/2003
Hikichi et al. 2009 ^{68,69}	EUS-FNA	Tumor seeding	0% (0/53)	53	0	The lack of seeding was reported by the secondary publication ⁶⁹ which had enrolled 53 patients between 1/2001 and 12/2003
Siddiqui et al. 2009 ⁷⁰	EUS-FNA	Any	0% (0/133)	133	0	—
Yusuf et al. 2009 ⁷¹	EUS-FNA	Mild pancreatitis	1.3% (11/842)	842	11	—
Zamboni et al. 2009 ⁷²	EUS-FNA	Any major complications	0% (0/545)	545	0	—
Zamboni et al. 2009 ⁷²	EUS-FNA	Abdominal fluid, no adverse consequences	0.4% (2/545)	545	2	—
Zamboni et al. 2009 ⁷²	EUS-FNA	Pain after the procedure, not clinically significant	1.1% (6/545)	545	6	—
Al-Haddad et al. 2008 ⁷³	EUS-FNA	Moderately severe abdominal pain within 2 hours, requiring hospital admission	1% (2/210)	210	2	—
Al-Haddad et al. 2008 ⁷³	EUS-FNA	Moderate abdominal pain requiring ER admission but no hospital stay and treated with oral analgesics	0.5% (1/210)	210	1	—
Al-Haddad et al. 2008 ⁷³	EUS-FNA	Any complications at 30 day follow-up	0% (0/210)	210	0	—
Ramirez-Luna et al. 2008 ⁷⁴	EUS FNA	Any	0% (0/52)	52	0	Evaluated for 4 hours after the procedure for complications
Sakamoto et al. 2008 ⁹⁵	EUS-FNA	Intra-abdominal abscess	0% (0/98)	98	0	—
Sakamoto et al. 2008 ⁹⁵	EUS-FNA	Bleeding from FNA site	0% (0/98)	98	0	—
Sakamoto et al. 2008 ⁹⁵	EUS-FNA	Increase in ascites	0% (0/98)	98	0	—
Sakamoto et al. 2008 ⁹⁵	EUS-FNA	Any other complications	0% (0/98)	98	0	—

Table C-16. Harms reported in included pancreas-specific studies (continued)

Study	Test	Harm	Rate	Number of Patients at Risk of Harm	Number of Patients Experienced Harm	Comments
Sakamoto et al. 2008 ⁹⁵	EUS-FNA	Seeding in the needle tract	0% (0/98)	98	0	–
Sakamoto et al. 2008 ⁹⁵	MDCT	Allergic eruption to contrast agent	1.9% (3/156)	156	3	–
Shah et al. 2008 ⁷⁵	EUS-FNA	periduodenal bleeding	0.8% (1/123)	123	1	Did not separate harms of EUS-FNA vs. EUS-FNA+TCB
Shah et al. 2008 ⁷⁵	EUS-FNA	Hematoma	0.8% (1/123)	123	1	Did not separate harms of EUS-FNA vs. EUS-FNA+TCB
Shah et al. 2008 ⁷⁵	EUS-FNA	Abdominal pain	1.6% (2/123)	123	2	Did not separate harms of EUS-FNA vs. EUS-FNA+TCB
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	Major complication: acute pancreatitis	0.9% (5/547)	547	5	–
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	Major complication: Severe pain	0.5% (3/547)	547	3	Post procedural
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	Major complication: Fever requiring intravenous antibiotics	0.4% (2/547)	547	2	–
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	Major complication: Reversal medication usage	0.2% (1/547)	547	1	–
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	Minor complication: sore throat	0.2% (1/547)	547	1	–
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	Minor complication: vomiting	0.2% (1/547)	547	1	–
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	Minor complication: abdominal pain	0.9% (5/547)	547	5	–
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	Minor complication: fever	0.2% (1/547)	547	1	–
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	Minor complication: exaggerated bleeding	0.4% (2/547)	547	2	–
Eloubeidi et al. 2007 ⁷⁶⁻⁸¹	EUS-FNA	Hypoxia from over sedation	0.3% (1/300)	300	1	This data point was reported by a secondary publication from this institution. ⁷⁹
Rocca et al. 2007 ⁸²	EUS-FNA	Major complications noted after procedures	0% (0/293)	293	0	–
Rocca et al. 2007 ⁸²	EUS-FNA	Mortality due to the procedure	0% (0/293)	293	0	–

Table C-16. Harms reported in included pancreas-specific studies (continued)

Study	Test	Harm	Rate	Number of Patients at Risk of Harm	Number of Patients Experienced Harm	Comments
Rocca et al. 2007 ⁸²	EUS-FNA	Minor intracystic hemorrhage	0.3% (1/293)	293	1	—
Rocca et al. 2007 ⁸²	EUS-FNA	Minor transient hyperthermia	0.3% (1/293)	293	1	—
Bournet et al. 2006 ⁸³	EUS-FNA	Mortality	0% (0/224)	224	0	—
Bournet et al. 2006 ⁸³	EUS-FNA	Any	2.2% (5/224)	224	5	—
Bournet et al. 2006 ⁸³	EUS-FNA	Pancreatitis	0.4% (1/224)	224	1	—
Bournet et al. 2006 ⁸³	EUS-FNA	Upper gastrointestinal bleeding	0.4% (1/224)	224	1	—
Bournet et al. 2006 ⁸³	EUS-FNA	Perforation, duodenal	0.4% (1/224)	224	1	—
Bournet et al. 2006 ⁸³	EUS-FNA	Infection	0.4% (1/224)	224	1	—
Bournet et al. 2006 ⁸³	EUS-FNA	Pleuropericarditis	0.4% (1/224)	224	1	—
Bournet et al. 2006 ⁸³	EUS-FNA	Complications related to celiac block procedures for anesthesia	0% (0/224)	224	0	—
Mahnke et al. 2006 ⁸⁴	EUS-FNA	Mild bleeding	0.3% (1/310)	310	1	Data not specific to those who received FNA
Mahnke et al. 2006 ⁸⁴	EUS-FNA	Moderate pancreatitis	0.3% (1/310)	310	1	Data not specific to those who received FNA
Mahnke et al. 2006 ⁸⁴	EUS-FNA	Unplanned primary care evaluation	0.6% (2/310)	310	2	Data not specific to those who received FNA
Mahnke et al. 2006 ⁸⁴	EUS-FNA	Unplanned emergency department evaluation	0.3% (1/310)	310	1	Data not specific to those who received FNA
Mahnke et al. 2006 ⁸⁴	EUS-FNA	Use of reversal agent	0.6% (2/310)	310	2	Data not specific to those who received FNA
Mahnke et al. 2006 ⁸⁴	EUS-FNA	Infection	0.6% (2/310)	310	2	Data not specific to those who received FNA
Wittmann et al. 2006 ⁸⁵	EUS-FNA	Any complications	0% (0/83)	83	0	The N of 83 represents those who received EUS-FNA alone of the pancreas

Table C-16. Harms reported in included pancreas-specific studies (continued)

Study	Test	Harm	Rate	Number of Patients at Risk of Harm	Number of Patients Experienced Harm	Comments
Mortensen et al. 2005 ⁸⁶	EUS-FNA	Acute pancreatitis	0.1% (1/670)	670	1	Full recovery with conservative treatment
Mortensen et al. 2005 ⁸⁶	EUS-FNA	Massive gastrointestinal bleeding	0.1% (1/670)	670	1	Happened 6 hours after procedure, patient died from massive gastrointestinal bleeding, Autopsy revealed disseminated cancer but no bleeding from EUS-FNA puncture areas
Ryozawa et al. 2005 ⁸⁷	EUS-FNA	Any complications	0% (0/52)	52	0	1 day of monitoring after the procedure
Ryozawa et al. 2005 ⁸⁷	EUS-FNA	Any complications	0% (0/52)	52	0	–
Ryozawa et al. 2005 ⁸⁷	EUS-FNA	Pancreatitis	0% (0/52)	52	0	–
Ryozawa et al. 2005 ⁸⁷	EUS-FNA	Hemorrhage	0% (0/52)	52	0	–
Ryozawa et al. 2005 ⁸⁷	EUS-FNA	Infection	0% (0/52)	52	0	–
Ryozawa et al. 2005 ⁸⁷	EUS-FNA	Tumor seeding	0% (0/52)	52	0	Authors reported this as “cancer dissemination”
Ryozawa et al. 2005 ⁸⁷	EUS-FNA	Perforation	0% (0/52)	52	0	–
Eloubeidi et al. 2004 ⁸⁸	EUS-FNA	Acute pancreatitis	0.64% (14/4,909)	4,909	14	Rate for 2 of 17 centers suggesting that the frequency of pancreatitis (0.26%) in retrospective cohort was underreported. Pancreatitis was classified as mild in 10 cases, moderate in 3 cases, and severe in 1 case. One death occurred after the development of pancreatitis but patient noted to have multiple co-morbid conditions and ultimate cause of death was deemed pulmonary embolism.
Gress et al. 2002 ⁸⁹	EUS-FNA	Acute pancreatitis	2% (2/100)	100	2	Occurred within four hours of EUS-FNA

Table C-16. Harms reported in included pancreas-specific studies (continued)

Study	Test	Harm	Rate	Number of Patients at Risk of Harm	Number of Patients Experienced Harm	Comments
Gress et al. 2002 ⁸⁹	EUS-FNA	Any complications other than acute pancreatitis	0% (0/100)	100	0	–
Harewood et al. 2002 ⁹⁰	EUS-FNA	Mild pancreatitis requiring 2-day hospital stay	0.5% (1/185)	185	1	–
Fritscher-Ravens et al. 2001 ⁹¹	EUS-FNA	Any	0% (0/114)	114	0	–
Gress et al. 2001 ⁹²	EUS-FNA	Substantial gastric mucosal bleeding with clot formation	2% (2/102)	102	2	Resolved spontaneously
Gress et al. 2001 ⁹²	EUS-FNA	Pancreatitis	1% (1/102)	102	1	Patient had history of pancreatitis and at the time was recovering from an attack
O'Toole et al. 2001 ⁹³	EUS-FNA	Acute pancreatitis	1.2% (3/248)	248	3	Complications occurred more frequently in cystic lesions
O'Toole et al. 2001 ⁹³	EUS-FNA	Aspiration pneumonia	0.4% (1/248)	248	1	Complications occurred more frequently in cystic lesions
Voss et al. 2000 ⁹⁴	EUS-FNA	Any	5.1% (5/99)	99	5	–
Voss et al. 2000 ⁹⁴	EUS-FNA	Bleeding	4% (4/99)	99	4	Intraprocedural
Voss et al. 2000 ⁹⁴	EUS-FNA	Abdominal pain and pyrexia, resolved spontaneously	1% (1/99)	99	1	–
Voss et al. 2000 ⁹⁴	EUS-FNA	Acute pancreatitis	0% (0/99)	99	0	–
Sakamoto et al. 2008 ⁹⁵	EUS-FNA	Abdominal pain, transient	2% (2/98)	98	2	–
Agarwal et al. 2004 ³⁵	Both MDCT and EUS-FNA	Abdominal pain	2.5% (2/81)	81	2	Post procedure pain that subsided completely within 24 hours. Complications were not reported separately for each test

AdenoCA=Adenocarcinoma; ER=emergency room; EUS-FNA=endoscopic ultrasound - fine needle aspiration; IPMN=intraductal papillary mucinous neoplasm; TCB=tru-cut biopsy

Table C-17. Harms from MRI in included non-pancreatic-cancer studies

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Semelka et al. 2013 ⁹⁶	Proof-of-concept	59	Patients with orders for brain or abdominal MRI scans	52 (range, 5–85)	52.5	0	Not applicable	Setting: Department of Radiology at a U.S. university hospital Timing: NR CA: gadobutrol (Gadavist; Bayer) vs. gadobenate dimeglumine (MultiHance; Bracco)
Albiin et al. 2012 ⁹⁷	Efficacy	31 31 patients received 0.8 g and 0.4 g, 30 patients received 0.2 g	Healthy	24.3 (range, 18–48)	56.2%	≥1 AE 25 (80.6%) at 0.8 g, 18 (58.1%) at 0.4 g, and 10 (33.3%) at 0.2 g ≥1 ADR 22 (71.0%) at 0.8 g, 13 (41.9%) at 0.4 g, and 7 (23.3%) at 0.2 g	Mild ADRs/AEs 32 at 0.8 g, 14 at 0.4 g, 6 at 0.2g Moderate ADRs/AEs 6 at 0.8 g, 1 at 0.4 g, 1 at 0.2 g Severe ADRs/AEs 1 at 0.8 g, 1 at 0.2 g Most common ADRs were diarrhea, nausea, headache and fatigue.	Setting: University hospital, Sweden Timing: Feb. to May 2010 CA: manganese chloride tetrahydrate (CMC-001) “Liver MRI using 0.8 g CMC-001 has the highest efficacy and still acceptable ADRs and should therefore be preferred.”

Table C-17. Harms from MRI in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Bredart et al. 2012 ⁹⁸	Prospective, non-randomized, multicenter	365	At risk for breast cancer	59.1% <50 years, 26.9% 50–59 years, 14% ≥60	0	NR	Significant MRI discomfort was due to immobility (37.5%), lying in the tunnel (20.6%), noise of the machine (64.6%), or panic feelings during MRI (6.1%).	Setting: 21 cancer centers, teaching hospitals, or private clinics in France Timing: Nov. 2006 to June 2008
Maurer et al. 2012 ⁹⁹	Post-marketing surveillance	84,621 50% neurological exams, 12.2% internal organs, 32.1% musculo-skeletal system, 2.3% MR angiographies, 4.9% not specified	19,354 (22.9%) were considered at risk 11.4% history of allergies, 6.6% hypertension, 2.3% CHD, 1.9% CNS disorders, 1.3% bronchial asthma, 1.3% beta-blocker treatment, 1.2% cardiac insufficiency, 0.9% renal failure, 0.8% history of allergic reaction to contrast medium, 1.3% liver dysfunction, 1.3% other	52.0±16.9	45.4	285 (0.34%) 421 AEs	65 different AEs were reported. 10 most common included nausea (0.2%), vomiting (0.1%) and less than 1% of patients had the following symptoms: pruritus, urticaria, dizziness, feeling of warmth, retching, sweating increased, paresthesia, and taste alteration. Serious AEs: 8 (<0.01%) 3 of these patients had life-threatening AEs, 1 of the 3 had inpatient treatment. “A causal relationship with GD-DOTA was considered probable in 1 patient, possible in 4 patients, and doubtful in 3 patients.”	Setting: 129 German radiology centers Timing: Jan. 2004 to Jan. 2010 CA: gadoteric acid (Gd-DOTA, Dotarem®), manually injected in 74.5%, automated injection in 25.5% Classification: WHO Adverse Reaction Terminology (1998) Allergies and history of allergic reaction to contrast medium were significantly associated (at 0.001 level) with increased risk of adverse events. Renal failure, liver dysfunction or betablocker intake were not associated with increased risk of adverse events.

Table C-17. Harms from MRI in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Voth et al. 2011 ¹⁰⁰	Integrated retrospective analysis (34 clinical studies)	4,549 Received gadobutrol (Gadovist/Gadavist) 1,844 received comparator contrast agents	Severe renal impairment: 38 gadobutrol, 5 comparator Moderate renal impairment: 328 gadobutrol, 132 comparator Mild renal impairment: 846 gadobutrol, 416 comparator Impaired liver function: 214 gadobutrol, 82 comparator Cardiovascular disease: 1,506 gadobutrol, 435 comparator History of allergies: 462 gadobutrol History of allergies to contrast agents: 33 gadobutrol	54.2±16.6 gadobutrol 54.7±14.5 comparator	58.5% gadobutrol 52.7% comparator	182 (4.0%) gadobutrol-related 74 of 1,844 (4.0%) related to comparators	Serious AEs: 21 17 (0.4%) gadobutrol, 4 (0.2%) comparator Drug-related serious AEs: 1 (<0.1%) gadobutrol	Setting: 55.3% Europe, 7.2% U.S./Canada, 7.7% South/Central America, 29.6% Asia, 0.3% Australia Timing: Trials conducted between 1993 and 2009 CA: gadobutrol (Gadovist/Gadavist); comparator contrast agents included gadopentetate dimeglumine (Magnevist, N= 912), gadoteridol (ProHance, N=555), gadoversetamide (OptiMark, N=227), or gadodiamide (Omniscan, N=150). Classification: MedDRA v. 12.1 “Gadobutrol was well tolerated by patients with impaired liver or kidney function, and by patients with cardiovascular disease.”

Table C-17. Harms from MRI in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Forsting and Palkowitsch 2010 ¹⁰¹	Integrated retrospective analysis (6 clinical studies)	14,299 14.7% MRA	NR	53.7	46.6	78 (0.55%) 82.4% occurred within 5 minutes of administration, 1 patient had an ADR 9 hours post-injection	Serious: 2 (0.01%) gadobutrol-related; 1 severe anaphylactoid reaction, 1 itching/swelling of throat Most frequently reported: nausea (0.25%)	Setting: 300 radiology centers in Europe and Canada Timing: 2000 to 2007 CA: gadobutrol “Gadobutrol 1.0M is well tolerated and has a good safety profile. The occurrence of ADRs observed following the intravenous injection of gadobutrol is comparable with the published data of other Gd-based contrast agents.”
Ichikawa et al. 2010 ¹⁰²	Multicenter, open-label, prospective Phase III	178	Suspected focal hepatic lesions	66 (range, 31–82)	72.4	44 (24.7%)	Mild: 56 Moderate: 6	Setting: 15 radiology departments in Japan Timing: Aug. 2001 to July 2003 CA: Combined unenhanced and gadoxetic acid disodium (Gd-EOB-DTPA)

Table C-17. Harms from MRI in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Ishiguchi and Takahashi 2010 ¹⁰³	Post-marketing surveillance	3,444	Liver disorder: 9.52% Kidney disorder: 2.85%	1% <15 years, 58.51% 15 to <65 years, 40.30% ≥65	49.45	32 (0.93%)	Mild: 36 (0.49% gastrointestinal-related disorders most commonly reported) Moderate: 4 2 patients with nausea, 2 with abnormal liver function	Setting: Department of Radiology at a medical university in Japan Timing: March 2001 to March 2005 CA: Gadoterate Meglumine (Gd-DOTA) “Statistically significant risk factors for experiencing adverse reactions were general condition, liver disorder, kidney disorder, complication, concomitant treatments, and Gd-DOTA dose.”
Leander et al. 2010 ¹⁰⁴	Crossover randomized	18	Healthy	25.0	100	19 AEs	19 mild gastrointestinal	Setting: Swedish university hospital Timing: NR CA: oral Manganese (MnCl ₂)
Hammerstingl et al. 2009 ¹⁰⁵	Multicenter, Phase III, randomized, inter-individually controlled comparison	572 292 gadobutrol, 280 gadopentetate	Patients with known focal lesions of the liver or suspected liver lesions	—	—	24 (4.2%) 10 (3.4%) gadobutrol, 21 (5.0%) gadopentetate	4 AEs definitely related to agents, 14 AEs possibly/probably related to agents No serious or severe AEs were reported.	Setting: 25 centers in 8 European countries Timing: NR CA: gadobutrol (Gadovist), gadopentetate (Magnevist)

Table C-17. Harms from MRI in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Shah-Patel et al. 2009 ¹⁰⁶	Retro-spective chart review	106,800 total 49,731 MRI	NR	Range 18–86	NR	15 (0.03)	<u>Mild</u> : 4 Itching or hives <u>Moderate</u> : 6 Vomiting: 3, Lightheaded sensation: 1 Fall: 1, Headache: 1 <u>Severe</u> : 1 Shortness of breath (before examination) <u>Others</u> : 4 Infiltrations at IV site: 2 Mild burns due to contact with magnetic resonance coil during the examination	Setting: Outpatient radiology in New York, NY Timing: over 4 years Total harms: 59 (0.06%) CA: gadopentetate dimeglumine (Magnevist; Berlex) Patients requiring assistance from emergency medical services: 18 (31%)

ADR=Adverse drug event; AE=adverse event; CA=contrast agent; CHD=coronary heart disease; CNS=central nervous system; Gd=gadolinium; Gd-DTPA=Gd-diethylenetriamine penta-acetic acid; MRA=magnetic resonance angiography; NR=not reported; NSF=nephrogenic systemic fibrosis

Table C-18. Harms from MDCT in included non-pancreatic-cancer studies

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Kim et al. 2013 ¹⁰⁷	Prospective cohort	1,048	Renal disease: 20 Cardiovascular disease: 38 Other allergic disease: 91	55.1±14.5	47.8	61 (5.8%)	<u>Immediate reactions:</u> Mild: 51 Moderate: 1 <u>Nonimmediate reaction:</u> Mild: 8 Moderate: 1	Setting: Seoul National University Bundang Hospital, Korea Timing: July to November 2010 Contrast medium (CM): 721 (68.8%) Iopromide, 323 (0.8%) Iomeprol, 3 (0.3%) Iohexol, and 1 (0.1%) Iodixanol “RCM skin testing for screening is of no clinical utility in predicting hypersensitivity reactions.”

Table C-18. Harms from MDCT in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Kim et al. 2013 ¹⁰⁷	Prospective cohort	1,048	Renal disease: 20 Cardiovascular disease: 38 Other allergic disease: 91	55.1±14.5	47.8	61 (5.8%)	<u>Immediate reactions:</u> Mild: 51 Moderate: 1 <u>Nonimmediate reaction:</u> Mild: 8 Moderate: 1	Setting: Seoul National University Bundang Hospital, Korea Timing: July to November 2010 Contrast medium (CM): 721 (68.8%) Iopromide, 323 (0.8%) Iomeprol, 3 (0.3%) Iohexol, and 1 (0.1%) Iodixanol “RCM skin testing for screening is of no clinical utility in predicting hypersensitivity reactions.”

Table C-18. Harms from MDCT in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Kobayashi et al. 2013 ¹⁰⁸	Retrospective cohort	36,472	Diabetes: 7,138 (19.5%) Hypertension: 10,461 (28.6%) Dyslipidemia: 5,972 (16.4%)	58.3	52	779 (2.1%)	<u>Acute adverse reactions (mild):</u> 756 Nausea/vomiting, rash, coughing/sneezing <u>Severe reactions:</u> 23 Shock, hypotension, desaturation, and airway obstruction	Setting: A community hospital in Tokyo, Japan Timing: April 2004 to March 2011 CM: non-ionic low-osmolar contrast agents such as iopamidol, iohexol, ioversol or iomeprol In multivariate logistic regression analysis, an adverse reaction history to contrast agents, urticaria, allergic history to drugs other than contrast agents, contrast agent concentration >70%, age <50 years, and total contrast agent dose >65 grams were significant predictors of an acute adverse reaction.

Table C-18. Harms from MDCT in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Davenport et al. 2012 ¹⁰⁹	Retrospective database review	24,826 injections of IV iopamidol 12,684 injections during warming period, 12,142 injections during no warming		51 (range, 1–79 years) period 1 52 (range 4–90 years), period 2	42% period 1, 28% period 2	177 (0.7%) Warming: 82 No warming: 95	<u>Iopamidol 300 (no warming): 69</u> Extravasations: 23 Allergic-like reactions: 46 (41 mild, 5 moderate) <u>Iopamidol 300 (warming): 74</u> Extravasations: 32 Allergic-like reactions: 42 (33 mild, 8 moderate, 1 severe [patient developed pulseless electric activity after injection and although use of CPR returned the patient to normal sinus rhythm, an infected sternotomy wound reopened, and became infected. The patient died 2 months later of complications related to the infected site.]) <u>Iopamidol 370 (no warming): 26</u> Extravasations: 18 Allergic-like reactions: 8 (6 mild, 2 moderate) <u>Iopamidol 370 (warming): 8</u> Extravasations: 5 Allergic-like reactions: 3 (all mild)	Setting: Duke University Medical Center, Durham, NC Timing: March 14, 2010 to April 19, 2011 (period 1), October 1, 2010 to April 19, 2011 (period 2) CM: Iopamidol 300 for CT exams, Iopamidol 370 for CT angiographic exams “Extrinsic warming (to 37° C) does not appear to affect adverse event rates for intravenous injections of Iopamidol 300 of less than 6 m/sec but is associated with a significant reduction in extravasation and overall adverse event rates for the more viscous Iopamidol 370.”

Table C-18. Harms from MDCT in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Jung et al. 2012 ¹¹⁰	Retrospective chart review	47,338	Medical history of 50 patients with cutaneous adverse reactions (CARs): 17 malignant neoplasm, 13 hypertension, 6 diabetes mellitus, 5 allergic history, 5 renal disease, 3 past adverse reactions to contrast medium, 2 tuberculosis, 2 hepatitis	0 to >80 years; focus on CARs occurring in 50 patients (age range 18 to 81)	58	62 (0.13%) 50 (80.7% of overall AEs) CARs	<u>Severe reactions</u> : 16 (25.8% of overall AEs) Dizziness, severe generalized urticaria, hypotension, and facial edema <u>Immediate CARs</u> : 46 (92% of CARs) Urticaria: 39 (78%) Angioedema: 5 (10%) Erythema: 1 (2%) Pruritus without rash: 1 (2%) <u>Delayed CARs</u> : 4 (8% of CARs) Maculopapular rash: 4 (8%)	Setting: Seoul, Korea Timing: Aug. 2005 to Nov. 2009 CM: nonionic monomers including iomeprol, iopamidol, iopromide, and ioversol
Kingston et al. 2012 ¹¹¹	Prospective cohort	26,854 CT and CTA (50)	Multiple clinical factors and comorbidities	NR	NR	119 (0.44%)	<u>Extravasations</u> : 119 (0.44%) 39 (0.34%) cannulations performed in the hospital, 80 performed prior Extravasation occurred at the elbow (71.4%), forearm (10.9%), wrist (6.7%) and hand (7.6%).	Setting: a hospital in Australia Timing: Sept. 2004 to April 2008 CM: nonionic IV (Ultravist 300) “Presence of cancer, hypertension, smoking and recent surgery was associated with higher extravasation rates.”

Table C-18. Harms from MDCT in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Mitchell et al. 2012 ¹¹²	Prospective consecutive cohort	633 174 CTPA for PE 459 non-CTPA	<u>CTPA:</u> Anemia: 11% DM: 19% History of hypertension: 54% Vascular disease: 15% Congestive heart failure: 12% Baseline renal insufficiency: 10% <u>Non-CTPA:</u> Anemia: 13% DM: 17% History of hypertension: 39% Vascular disease: 8% Congestive heart failure: 5% Baseline renal insufficiency: 10%	CTPA: 50±16 Non-CTPA: 46±15	CTPA: 34 Non-CTPA: 46	–	<u>CIN</u> CTPA: 25 (14%, 95% Confidence Interval 10% to 20%) Non-CTPA: 45 (9.8%) <u>Severe renal failure:</u> 3 CTPA <u>Death from renal failure:</u> 2 CTPA <u>All-cause 45-day mortality rate:</u> 15 CTPA: 6 (3%), death due to renal failure (6), patients with CIN (4) Non-CTPA: 9 (2%)	Setting: a large U.S. academic tertiary care center Timing: June 2007 to January 2009 CM: NR “Development of CIN was associated with an increased risk of death from any cause (relative risk = 12, 95% Confidence Interval: 3 to 53).”

Table C-18. Harms from MDCT in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Vogl et al. 2012 ¹¹³	Observational, non-interventional, prospective, multicenter	10,836	5,033 (46.4%) had 1 to 7 concomitant diseases (including DM (6.9%) and renal insufficiency (0.9%) that could potentially influence tolerability of ioversol	60.9	48.1	30 (0.28%)	<u>Mild</u> : 26 Urticaria: 13 Nausea: 11 Erythema: 6 <u>Serious</u> : 4 Anaphylactoid adverse reactions requiring hospitalization: 3 Patients with ≥1 AE: 30	Setting: 72 centers in Germany Timing: August 2006 to April 2007 CM: ioversol
Cadwallader et al. 2011 ¹¹⁴	Prospective audit	198 scans	Pancreatitis: 5.2% Biliary pathology: 11.2% Appendicitis: 12.6% Bowel obstruction: 9% Peptic ulcer disease: 3.2% Diverticular disease: 6.6% Postoperative complications: 3.6% No diagnosis: 13.2% Transferred specialty: 4.6% Other 30.8%	50.4 (range, 16–94)	44.4	41 (20.7%) scans didn't alter management and were deemed as unnecessarily exposing patients to CT radiation	Risk of fatal cancer induction female aged: 20: 1 in 1,675 30–50: 1 in 2,452 60: 1 in 3,070 70: 1 in 4,113 80: 1 in 7,130 Risk of fatal cancer induction male aged: 30–50: 1 in 2,523 60: 1 in 3,897 80: 1 in 4,289	Setting: Tertiary referral surgical unit Timing: March–May 2008 “The potential diagnostic benefits must outweigh the risks. Figures from the U.S. from 2007 suggest 19,500 CT scans were undertaken each day – the equivalent radiation dose of up to 5,850,000 chest radiographs.”

Table C-18. Harms from MDCT in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Hatakeyama et al. 2011 ¹¹⁵	Retrospective chart review	50 (64 CTAs)	Peritoneal Dialysis	55.0±13.1	68	2 (0.04%)	<u>Mild:</u> 1 Skin disorder <u>Serious:</u> 1 Atrial fibrillation	Setting: A hospital and research institute in Japan Timing: 2002 to 2009 CM: Iopamidol, a low osmolar nonionic
Loh et al. 2010 ¹¹⁶	Prospective surveillance	539 258 iohexol (51 CTA, 209 CT) 281 control (un-enhanced CT)	NR	53.05±14.9	57.7% iohexol 46.9% control	87 (16.1%) 76 (29.4%) iohexol 11 (3.9%) Control	Delayed adverse reactions (DAR) 37 (14.3%) iohexol, 7 (2.5%) control; p<0.0001 Skin rashes or itching Iohexol: 13 (5.0%), Control: 2 (0.71%); P=0.00273 Patients with cutaneous DARs Iohexol: 26 (10.1%), Control: 2 (0.71%); P<0.0001 Skin redness (p=.0055), skin swelling (p=.0117) and headache (p=.0246) also occurred statistically more frequently in the iohexol group.	Setting: Tertiary academic medical center Timing: 2006 to 2008 CM: iohexol “This study substantiates a frequent occurrence of DARs at contrast-enhanced CT compared with that in control subjects.”

Table C-18. Harms from MDCT in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Ozbulbul et al. 2010 ¹¹⁷	Prospective	52 MDCT coronary angiography	Suspected coronary artery disease	56.4±13.6 iodixanol (N=28) 54.1±17.1 iopamidol (N=24)	38	32 (61.5%)	<u>Moderate:</u> 32 (61.5%) Intense injection-related heat: Iodixanol: 11 (39.3%) Iopamidol: 20 (83.3%) Nausea: Iodixanol: 1 (3.5%), Iopamidol: 6 (25%) Dizziness: Iodixanol: 0, Iopamidol: 3 (12.5%)	Setting: radiology department, Turkey Timing: Jan. 2008 to June 2008 CM: iopamidol 370 (a low-osmolar) vs. iodixanol 320 (an iso-osmolar) “Iodixanol 320 causes less frequent sensation of heat on intravenous injection. This means more comfort and success in following the breath-hold commands of patients during scanning.”
Shah-Patel et al. 2009 ¹⁰⁶	Retrospective chart review	106,800 total 33,321 CT	NR	Range 18–86	NR	35 (0.10%)	<u>Mild:</u> 17 Itching or hives, most often related to iodine-based intravenous contrast injections <u>Moderate:</u> 7 Falls: 3, Nasal congestion: 1, Nausea: 2 Dizziness: 1 <u>Severe:</u> 5 Shortness of breath after IV injection: 5 <u>Others:</u> 6 Infiltrations at IV site: 5, Hematoma at IV site: 1	Setting: Outpatient radiology center in New York, NY Timing: over 4 years CM: iopromide (Ultravist 300)

CECT=Contrast-enhanced computed tomography; CIN=contrast-induced neuropathy; CPR=cardiopulmonary resuscitation; CTA=CT angiography; CTPA=CECT of the pulmonary arteries; PE=pulmonary embolism; SCr=serum creatinine

Table C-19. Harms from EUS in included non-pancreatic-cancer studies

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events (%)	Notes
Coté et al. 2010 ¹¹⁸	Prospective analysis of sedation-related complications	799 423, EUS, 336 ERCP, and 40 small-bowel enteroscopy	NR 60.5% patients classified as ASA Class III or higher (severe systemic disease, not incapacitating), 0.5% had a Mallampati score equal to 4	57.8±16.5	46.6	115 (14.4%)	Airway modifications (AMs): 154 events (115 patients); 1 AM in 88 (76.5%) patients, 2 AMs in 15 (13.1%) patients, 3 AMs in 12 (10.4%) patients Hypoxemia (SpO ₂ <90%): 102 (12.8%) Hypotension requiring vasopressors: 4 (0.5%) Procedure termination: 5 (0.6%)	Setting: One tertiary care medical center in St. Louis, MO Timing: Procedures from May 2008 to November 2008 In multivariate analysis, male gender (Odds Ratio (OR) 1.75 (95% Confidence Interval (CI): 1.08 to 2.85; p=0.02), ASA class ≥3 (OR 1.90 (95% CI: 1.11 to 3.25; p=.02) and body mass index (OR 1.05 (95% CI: 1.01 to 1.09; p=0.009) were independent predictors of AMs.

C-19. Harms from EUS in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events (%)	Notes
Eloubeidi et al. 2009 ¹¹⁹	Prospective study of frequency and management of cervical esophageal perforation-EUS by a single experienced endo-sonographer	4,894 patients underwent upper EUS procedures	Indications for EUS: Pancreaticobiliary (58%) Esophageal (14%) Mediastinal (14%) Gastric (9%) Celiac blocks (1%) Other (4%)	59.7 ±14.3	54	3 (0.06%)	Cervical esophageal perforation (3 patients) at the time of intubation with EUS 1 of 3 patients reported chest pains, 2 of 3 patients had excessive salivation and sore throat 1 of 3 patients showed crepitus at bedside exam	Setting: One University Hospital, Birmingham, AL Timing: July 2000 to July 2007 All patients were immediately admitted, underwent surgical repair with neck incision and recovered completely. All patients resumed swallowing without complications.
Kalaitzakis et al. 2011 ¹²⁰	Retrospective case control	4,624	NR	60	43% of patients with unplanned events*	9 (0.2%)	Allergic reaction to sedation:3 Desaturation: 2 Supraventricular tachycardia: 2 Duodenal perforation: 1 Gallbladder perforation: 1 Patients admitted to hospital: 4	Setting: One tertiary referral centre in London, United Kingdom Timing: January 2001 to December 2007

C-19. Harms from EUS in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events (%)	Notes
Niv et al. 2011 ¹²¹	Retrospective review of physician reporting Focus on severe events	10,647 ERCP and EUS	NR	69.3±14.3	21.4%	42 (.4%) serious adverse events According to Heinrich's Iceberg model, the authors estimate 957 adverse events with minor damages and 9900 adverse events with marginal damage or no damage.	<u>Serious: 42 (EUS, ERCP)</u> Perforation: 29 (69%) Bleeding: 2 (4.8%) Cardiovascular and respiratory event: 1 (4.8%) Teeth trauma: 2 (2.4%) Other: 8 (19.0%) Outcome: Residual damage: 18 (42.9%) Complete healing: 6 (14.3%) Death: 15 (35.7%) Unknown: 3 (7.1%)	Setting: Israel health institutes covered by one insurer Timing: 7 year period (2000 to 2006)

C-19. Harms from EUS in included non-pancreatic-cancer studies (continued)

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events (%)	Notes
Schilling et al. 2009 ¹²²	Prospective randomized Focus on sedation-related AEs	151 Midazolam/meperidine group: 75 (19 EUS) Propofol: 76 (15 EUS)	<u>Midazolam</u> Bile duct stone: 24 (32%) Exclusion of bile duct stones: 10 (13%) Pancreatic cancer: 10 (13%) Other: 42% <u>Propofol</u> Bile duct stone: 22 (29%) Exclusion of bile duct stones: 8 (10%) Pancreatic cancer: 12 (16%) Other: 45% 47.6% ASAIII 17.8% ASA IV	Midazolam: 83.2 (range 80–96) Propofol: 82.4 (range 80–92)	Midazolam: 35 Propofol: 33	30 overall; not reported by device	<u>Minor: 30 (EUS, ERCP, and DBE)</u> Hypoxemia (minor events): 16 7 Midazolam, 9 Propofol Bradycardia: 8 3 Midazolam, 5 Propofol Arterial hypotension: 6 2 Midazolam, 4 Propofol Overall complication rate Midazolam: 16% Propofol: 23.7%, p>0.05	Setting: Diakonie Hospital Mannheim, Mannheim, Germany Timing: March 2006 to June 2007

* Unplanned events defined as any deviation from the preprocedure plan including adverse events as a result of the direct effect of the endoscope on sites or organs transversed or treated during the procedure (e.g, perforation); indirect effects in organs not directly involved in the procedure (e.g., heart); equipment malfunction; or sedation issues

AE=Adverse events; ASA=American Society of Anesthesiologists; ERCP=endoscopic retrograde cholangiopancreatography; EUS=endoscopic ultrasound; NR=not reported

Table C-20. Harms from PET/CT in included non-pancreatic-cancer studies

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Shah-Patel et al. 2009 ¹⁰⁶	Retrospective chart review	106,800 total 3,359 PET/CT	NR	Range 18-86	NR	5 (0.14)	<u>Mild: 1</u> Itching or hives <u>Severe: 4</u> Chest pain: 2 (1 before exam and 1 after FDG injection) Shortness of breath after IV injection: 2 (1 patient was premedicated for a known allergy to IV contrast)	Setting: Outpatient radiology in New York, NY Timing: over 4 years Total harms: 59 (0.06%) Patients requiring assistance from emergency medical services: 18 (31%)

F18-FDG=Fluorine-18-labeled fluorodeoxyglucose; NR=not reported

Table C-21. Harms from EUS-FNA in included non-pancreatic-cancer studies

Study	Study Design	N Patients	Diagnosis	Age, Years (Mean±SD)	% Male	N Harmed (%)	Adverse Events	Notes
Katanuma et al. 2013 ⁴⁵	Retrospective database review	316	Pancreatic cancer: 4 PNET: 3 Chronic pancreatitis: 1	66.5±11.5 (range, 23–92)	54	11 (3.4%)	Pancreatitis: 6 (1 moderate, 5 mild) Abdominal pain: 4 (mild) Bleeding: 1 (mild)	In univariate analysis, tumors ≤20 mm in diameter (p<0.001), PNETs (p=0.012) and procedures using an increased length of needle penetration (e.g., the puncture needle had to traverse normal pancreatic tissue) (p=0.048) were statistically significantly associated with complications. In multivariate analysis, tumors measuring ≤20 mm in diameter (OR 18.48; 95% CI 3.55 to 96.17; p<0.001) and PNETs (OR 36.50; 95% CI 1.73 to 771.83; p=0.021) were significant independent risk factors.

CI=Confidence interval; OR=odds ratio; PNET=pancreatic neuroendocrine tumors

Table C-22. Physical and chemical characteristics of all currently marketed Gadolinium agents for MRI

Generic Name	Trade Name	Company	Acronym	Charge	Type	Dose (mml/kg)	Concentration (M)
Gadobenate dimeglumine	Multihance	Bracco	Gd-BOPTA	Di-ionic	Liver-specific	0.1	0.5
Gadobutrol	Gadovist	Bayer-Schering	Gd-BT-DO3A	Nonionic	ECF	0.1	1.0
Gadoterate meglumine	Dotarem	Guerbet	Gd-DOTA	Ionic	ECF	0.1	0.5
Gadopentetate dimeglumine	Magnevist	Bayer-Schering	Gd-DTPA	Di-ionic	ECF***	0.1	0.5
Gadodiamide	Omniscan	GE-Healthcare	Gd-DTPA-BMA	Nonionic	ECF	0.1	0.5
Gadoversetamide	OptiMark	Covidien	Gd-DTPA-BMEA	Nonionic	ECF	0.1	0.5
Gadoxetic acid disodium salt	Primovist*	Bayer-Schering	Gd-EOB-DTPA	Di-ionic	Liver-specific	0.025	0.25
Gadoteridol	Prohance	Bracco	Gd-HP-DO3A	Nonionic	ECF	0.1	0.5
Gadofosveset trisodium	Vasovist**	EPIX/Lantheus Medical Imaging	MS325	Tri-ionic	Blood-pool	0.03	0.25

* Tradename is Primovist in Europe and Asia but Eovist in USA.

** Tradename is Ablavar in USA and Canada.

***ECF=Extracellular fluid

Taken from Chang et al.¹²³

Screening Studies

Table C-23. General study information of screening studies

Study	Country	Location	Dates	Prospective or Retrospective	Funding Source and Disclosed Potential Conflicts of Interest	Length of Follow-up	How was Reference Standard Determined?	Comments
Canto et al. 2012 ¹²⁴	USA	Johns Hopkins University, Brigh Dana Farber, Mayo Clinic, MD Anderson, UCLA	NR	Prospective	NCI, Lustgarten Foundtn, Folfe Foundtn, Olympus, Cook Med, Karp Fund, ChiRho; no COIs	Average 2.4 years	NR	CAPS 3
Al-Sukhni et al. 2012 ¹²⁵	Canada	Univ Toronto	2003–2011	Prospective	Pancreas Cancer Canada, NIH-PACGENE (grant); Princess Margaret Hosp Found Fund; COIs not mentioned	Average 4.2 years	NR	–
Verna et al. 2010 ¹²⁶	USA	Columbia/NY Prebs	NR	Prospective	Grant from Hirshberg Foundation; no COIs	NR	NR	–
Langer et al. 2009 ¹²⁷	Germany	Philips Univ, Marburg	June 2002–December 2007	Prospective	Deutsche Krebshilfe (grant); no COI	NR	NR	–
Vasen et al. 2011 ¹²⁸	Netherlands	Leiden Univ Med Center	Jan 1 2000–Jan 1 2010	Prospective	ZonMW (org that supports govt), no COI	Average 4 years	NR	–
Canto et al. 2006 ^{129,130}	USA	Johns Hopkins University	2001–2004	Prospective	NCI grant, Rolfe found, Rangos Charit Fund, Clayton Fund, NIH grant; no COI mentioned	NR	NR	CAPS 2

Table C-24. Patient characteristics of screening studies

Study	Patient Enrollment Criteria	Number of Control not Included in the Included pt	Number of Patients Included//Imaged	Number Female	Mean Age	PJS	Breast/Ovarian Cancer	FPC (not Specified, # Relatives)	FPC (≥2 Relatives)	FPC (≥3 Relatives)	Fam Hx Panc Cancer- 2 FDR+	Fam Hx panc Cancer - Other	p16 Mutation	STK11 mut	BRCA1/2 Combined	BRCA 1 mut	BRCA 2 mut	Hered Pancreatitis	FDR of Mult Prim Cancer pt Including	HNPCC	FAMM	Other non-panc Cancers
Canto et al. 2012 ¹²⁴	HRI at any of 5 sites	–	216	116	56.1	2	19	–	75	120	–	–	–	–	–	–	–	–	–	–	–	–
Al-Sukhni et al. 2012 ¹²⁵	HRI	–	175 included, 262 imaged*	173	NR	7	–	–	159	–	–	–	11	–	–	5	68	2	10	–	–	–
Verna et al. 2010 ¹²⁶	Family history of pancreatic cancer, interest in risk of disease	3 avg risk; 14 mod; 32 high risk	41**	33	52	–	–	34	–	–	15	35	–	–	17	–	–	–	–	3	3	31
Langer et al. 2009 ¹²⁷	In a registry of high-risk family members	–	76	NR	60	–	–	–	44	32	–	–	–	–	–	–	2	–	–	–	–	–
Vasen et al. 2011 ¹²⁸	Dutch FAMM registry	–	79	48	56	–	–	–	–	–	–	37	79	–	–	–	–	–	–	–	–	–
Canto et al. 2006 ^{129,130}	High risk of Peutz-Jeghers syndrome or familial pancreatic cancer	149 (mean 54 yo, 69 F)	78	44	52	6	–	72	–	–	–	–	–	–	–	–	–	–	–	–	–	–

* 30 withdrew, 6 no MRI (claustrophobia, pacemaker)

**10 neither EUS/MRI, 2 avg risk, 3 hr (young and one in tx for breast/ov ca); 5mod pt pref and young age of affected fam member

Table C-25. General test details of screening studies

Study	Imaging Test(s) of Interest	Order of Tests Performed	Number of Test Readers	Prior Experience of These Readers	Other Reported Details About the Readers	Number of Patients in This Study who Received This Test	If EUS-FNA, how Many Patients Received FNA?
Canto et al. 2012 ¹²⁴	MDCT, MRI, EUS +/- FNA	EUS+/-FNA always last	NR	"highly experienced radiologists and GI at 5 tertiary AMCs"	"blinded to results of other imaging tests"	216	12
Al-Sukhni et al. 2012 ¹²⁵	MRI annually (+/- CT/EUS/FNA)	MRI first	1	"MRI experienced"	blinded to pt risks	33 received MRI; NR the Ns for other tests	NR
Verna et al. 2010 ¹²⁶	MRI, EUS +/- FNA	NR	NR	"a radiologist experienced in panc imaging, blinded to pt cancer risks"	NR	31 EUS-FNA, 7 ERCP, 33 MRI	6
Langer et al. 2009 ¹²⁷	MRA/MRCP, EUS +/- FNA	NR	1	"experienced investigator"	NR	NR	NR
Vasen et al. 2011 ¹²⁸	MRI	NR	NR	NR	NR	NR	NA
Canto et al. 2006 ^{129,130}	MDCT, EUS +/- FNA	EUS first, if abnormal then ERCP on separate visit	1	EUS-FNA: "experienced endosonographer"; ERCP: "experienced endoscopist"; CT: experienced CT radiologist unaware of EUS or ERCP findings	EUS-FNA was blinded to CT results	65 ERCP, NR the Ns for other tests	NR

Table C-26. CT details of screening studies

Study	MDCT: 4 vs. 16 vs. 64 Detector row or Other	MDCT: Slice Thickness (if NR, Then Record Machine Name)	MDCT: Whether Reformats Used (Coronal Sagittal) or Only Axial	MDCT: Contrast Y or N	MDCT: Type of Contrast	MDCT: Phases of Enhancement Dynamic vs. Routine; Arterial/Portal Venous/Equilibrium Means Dynamic
Canto et al. 2012 ¹²⁴	NR	0.5 and 3 mm	Axial, multiplanar, 3D rendering	Y	100-120 mL Omnipaque-350 or Visipaque-350	Dual phase 30 and 60s
Al-Sukhni et al. 2012 ¹²⁵	NR	NR	NR	NR	NR	NR
Verna et al. 2010 ¹²⁶	–	–	–	–	–	–
Langer et al. 2009 ¹²⁷	–	–	–	–	–	–
Vasen et al. 2011 ¹²⁸	–	–	–	–	–	–
Canto et al. 2006 ^{129,130}	Spiral	1.24 mm	3D recon	Y	120 mL of Omnipaque-350	Dual phase

Table C-27. EUS-FNA details of screening studies

Study	EUS FNA Technology	EUS-FNA Needle Type	EUS-FNA Needle Size	Other EUS-FNA Details
Canto et al. 2012 ¹²⁴	Olympus GFUM20 or GFUE160-AL5) and Olympus CFUC140P, SSD-Alpha5, or Alpha10)	NR	NR	–
Al-Sukhni et al. 2012 ¹²⁵	NR	NR	NR	–
Verna et al. 2010 ¹²⁶	GRUC140P and SSD-Alpha 5 Olympus	NR	NR	–
Langer et al. 2009 ¹²⁷	Pentax FG 32 UA	EUS bx needle, mult passes	21 G	“followed standardized procedure,” cytology by experienced pathologist
Vasen et al. 2011 ¹²⁸	–	–	–	–
Canto et al. 2006 ^{129,130}	Olympus UM-130 or UM-160 radial and linear FG UCT1409-AL5	u/s aspiration needle wilson-cook	22G	Onsite cytopathologist review; also indept review by experienced cytopath unaware of clinical/radiologic findings

Table C-28. MRI details of screening studies

Study	MRI: Magnet Strength	MRI: Contrast Y or N	MRI: Type of Contrast	MRI: Phases of Enhancement Dynamic vs. Routine; Arterial/Portal Venous/Equilibrium Means Dynamic	MRI: Diffusion-Weighted Y or N	MRI: Type of Coil (Body/Pelvic or Endorectal)
Canto et al. 2012 ¹²⁴	1.5 T	Y	Human secretin and gadolinium	Arterial, portal venous, delayed phases (20s, 70s, 3m)	Y- T1/T2	Phased-array torso coil
Al-Sukhni et al. 2012 ¹²⁵	1.5 T	N	X	x	T2 weighted	4-8 surface array coil
Verna et al. 2010 ¹²⁶	1.5 T	Y	Gadodiamide or gabobenate dimeglumine	–	T2	Body
Langer et al. 2009 ¹²⁷	1.5 T	Both	Magnevist and panc-spec Teslascan	Dynamic enhanced	T2/T1	–
Vasen et al. 2011 ¹²⁸	1.5 T	Y	Gadolinium dotarem	–	T2ax	Phased array torso coil
Canto et al. 2006 ^{129,130}	–	–	–	–	–	–

Table C-29. General data reported by screening studies for any imaging modality

Study	# HRI who Received Imaging	# HRI who had no Positive Imaging Throughout the Study	# HRI who had at Least one Positive Image, but not Concerning Enough to Result in Surgery or Biopsy (i.e., Pathological Study)	# who had at Least one Positive Image, and Received Either Surgery or Biopsy	True Positive (Pathology Confirmed Cancer)	Major False Positive (Surgery Indicated Benign Lesion)	Minor False Positive (Biopsy Indicated Benign Lesion, Therefore Surgery Avoided)	False Negative (Initial Imaging Missed Cancer, but Later Pathology Showed Cancer)
Canto et al. 2012 ¹²⁴	216	124	87	5	3	2	0	0
Al-Sukhni et al. 2012 ¹²⁵	175	91	78	6	2	2	0	2
Verna et al. 2010 ¹²⁶	41	NR	NR	6	2	4	0	0
Langer et al. 2009 ¹²⁷	76	48	14	14	0	7	NR	0
Vasen et al. 2011 ¹²⁸	67	NR	NR	7	6	0	0	1
Canto et al. 2006 ^{129,130}	78	NR	NR	8	4	4	0	0

HRI=High risk individuals; NR=not reported

Table C-30. Screening studies: individual patient data for patients whose final diagnosis was based on surgery and/or biopsy

Study	Patient Age	Patient Risk	Patient Follow-up (Months)	# Year Lesion Found	CT Dx	MRI/MRCP Dx	EUS Dx	ERCP Dx	Final Pathology Dx	Final Procedure Performed	Follow-up
Canto et al. 2012 ¹²⁴ Patient 1	73	2FDR	NR	1	BD-IPMN	BD-IPMN	Combined IPMN w 3.8 mural nodule	NA	MD-IPMN, mult PanIN (grade 3)	Distal pancreatectomy	NR
Canto et al. 2012 ¹²⁴ Patient 2	65	2FDR	NR	1	BD-IPMN	BD-IPMN	BD-IPMN w 5.5 mural nodule	NA	MD-IPMN, mult PanIN (grade 2)	Pancreaticoduodenectomy	NR
Canto et al. 2012 ¹²⁴ Patient 3	67	2FDR	NR	1	BD-IPMN	BD-IPMN	Mult BD-IPMN, PNET	NA	BD-IPMN (low); multi PanIN (grade 3), mult PNET	Total pancreatectomy	NR
Canto et al. 2012 ¹²⁴ Patient 4	72	2FDR	NR	1	BD-IPMN	BD-IPMN	BD-IPMN	NA	BD-IPMN (MGD); multi PanIN (grade 2)	Distal pancreatectomy	NR
Canto et al. 2012 ¹²⁴ (study averages) Patient 5	61	1 FDR, 1 SDR, BRCA2, FBOC	NR	1	No lesion, nl pancr	No lesion, nl pancr	BD-IPMN	NA	BD-IPMN (LGD), multi PanIN (grade 2)	Distal pancreatectomy	NR

Table C-30. Screening studies: individual patient data for patients whose final diagnosis was based on surgery and/or biopsy (continued)

Study	Patient Age	Patient Risk	Patient Follow-	# Year Lesion Found	CT Dx	MRI/MRCP Dx	EUS Dx	ERCP Dx	Final Pathology Dx	Final Procedure Performed	Follow-up
Study averages for Canto et al. Patients 1–5 (above), patient follow-up = 28.8 Months	–	–	–	–	–	–	–	–	–	–	–

Table C-30. Screening studies: individual patient data for patients whose final diagnosis was based on surgery and/or biopsy (continued)

Study	Patient Age	Patient Risk	Patient Follow-	# Year Lesion Found	CT Dx	MRI/MRCP Dx	EUS Dx	ERCP Dx	Final Pathology Dx	Final Procedure Performed	Follow-up
Al-Sukhni et al. 2012 ¹²⁵ Patient 1	57	1 FDR, 1 SDR panc ca	NR	4	NR	1.5 cm mass	NR	NA	Adenocarcinoma	Total pancreatectomy	30 months dz free, then local recurrence and died metastatic 6 months later
Al-Sukhni et al. 2012 ¹²⁵ Patient 2	81	1 FDR, 2 SDR panc ca	NR	1	Normal- no cut off sign	Mult cysts, cut off head of panc periph duct	Before performed, weight loss jaundice, patient metastatic	NA	Adenocarcinoma	Percutaneous biopsy for metastatic disease	Within 2 months metastatic, 6 months died
Al-Sukhni et al. 2012 ¹²⁵ Patient 3	65	BRCA2mut, 1 FDR	NR	5, patient missed year 4 exam	NR	3 cm mass	NR	NA	Adenocarcinoma	Biopsy	Liver mets, chemo
Al-Sukhni et al. 2012 ¹²⁵ Patient 4	66	–	NR	1	NR	hypervasc lesion head of panc	NR	NA	Neuroendocrine tumor	Pancreatico- duodenectomy	6 years disease free
Al-Sukhni et al. 2012 ¹²⁵ Patient 5	54	2 FDR,h/o uter canc	NR	1	NR	BD-IPMN x 2	NR	NA	PanIN-1a to PanIN-2	Distal pancreatectomy	Stable
Al-Sukhni et al. 2012 ¹²⁵ Patient 6	54	1 FDR, 2 SDR panc ca	NR	1	NR	NR	BD-IPMN dysplastic cells	NA	BD-IPMN low- grade dysplasia, no cancer	Distal pancreatectomy (lap)	Stable
Study averages for Al-Sukhni et al. Patients 1–6 (above), patient follow-up = 50.4 Months	–	–	–	–	–	–	–	–	–	–	–
Verna et al. 2010 ¹²⁶ Patient 1	58	High	NR	1	NA	Mass with liver lesions	Mass with liver lesions	NR	Stage 4 pancreatic adenocarcinoma	FNA	NR

Table C-30. Screening studies: individual patient data for patients whose final diagnosis was based on surgery and/or biopsy (continued)

Study	Patient Age	Patient Risk	Patient Follow-	# Year Lesion Found	CT Dx	MRI/MRCP Dx	EUS Dx	ERCP Dx	Final Pathology Dx	Final Procedure Performed	Follow-up
Verna et al. 2010 ¹²⁶ Patient 2	61	High	NR	1	NA	NR	2cm mass	NR	Pancreatic carcinoma w IPMN and PanIN2	total pancreatectomy	NR
Verna et al. 2010 ¹²⁶ Patient 3	47	High	NR	1	NA	NR	IPMN, irregular PD	IPMN, irregular PD	IPMN-B w mod dysplasia, mult PanIN2	distal pancreatectomy	NR
Verna et al. 2010 ¹²⁶ Patient 4	56	High	NR	1	NA	NR	IPMN-B	IPMN-B	NR	distal pancreatectomy	NR
Verna et al. 2010 ¹²⁶ Patient 5	40	Mod	NR	1	NA	IPMN-B	IPMN-B	NR	NR	distal pancreatectomy	NR
Verna et al. 2010 ¹²⁶ Patient 6	45	Mod	–	1	NA	NR	1 cyst, elv cyst fluid	NR	Cyst, IPMN-B mod dysp, focal PanIN2	central pancreatectomy	NR
Study averages for Verna et al. Patients 1–6 (above), patient follow-up = NR	–	–	–	–	–	–	–	–	–	–	–

Table C-30. Screening studies: individual patient data for patients whose final diagnosis was based on surgery and/or biopsy (continued)

Study	Patient Age	Patient Risk	Patient Follow-	# Year Lesion Found	CT Dx	MRI/MRCP Dx	EUS Dx	ERCP Dx	Final Pathology Dx	Final Procedure Performed	Follow-up
Langer et al. 2009 ¹²⁷ Patient 1	NR	FPC	NR	NR	NA	hypointens e mass tail	diffuse changes, tail + hyperechoic nodule	NA	FNA- normal	FNA	NR
Langer et al. 2009 ¹²⁷ Patient 2	NR	FPC	NR	NR	NA	hypointens e mass tail	diffuse changes, tail + hyperechoic nodule	NA	FNA- normal	FNA	NR
Langer et al. 2009 ¹²⁷ Patient 3	NR	MPCS	NR	NR	NA	Normal	heterogenous mass, tail	NA	FNA- normal	FNA	NR
Langer et al. 2009 ¹²⁷ Patient 4	NR	FPC	NR	NR	NA	Normal	diffuse changes, tail	NA	FNA- normal	FNA	NR
Langer et al. 2009 ¹²⁷ Patient 5	NR	FPC	NR	NR	NA	Normal	diffuse changes, tail extrapanc nod	NA	FNA- normal	FNA	NR
Langer et al. 2009 ¹²⁷ Patient 6	NR	MPCS	NR	NR	NA	Normal	diffuse changes, tail hyperechoic lesion	NA	FNA- normal	FNA	NR
Langer et al. 2009 ¹²⁷ Patient 7	NR	FPC	NR	NR	NA	Normal	diffuse chnages, tail	NA	FNA- normal	FNA	NR
Langer et al. 2009 ¹²⁷ Patient 8	NR	Mod	93	NR	NA	Negative (panc), 2liver lesions	hypoechoic mass (head)	NA	No panc tumor, foc nodular hyperplasia in liver	Exploration, liver wedge resection	Incisional hernia
Langer et al. 2009 ¹²⁷ Patient 9	61	Mod	51	NR	NA	Negative	hypoechoic mass	NA	Serous oligocystic adenoma	Distal pancreatectomy + splenectomy	No pathologies
Langer et al. 2009 ¹²⁷ Patient 10	61	High	60	NR	NA	Cystic lesion (head and tail)	Cystic lesion (head and tail)	NA	Serous oligocystic adenoma, lobular fibrosis PanIN1	Distal pancreatectomy + splenectomy	Cystic lesion prev known

Table C-30. Screening studies: individual patient data for patients whose final diagnosis was based on surgery and/or biopsy (continued)

Study	Patient Age	Patient Risk	Patient Follow-	# Year Lesion Found	CT Dx	MRI/MRCP Dx	EUS Dx	ERCP Dx	Final Pathology Dx	Final Procedure Performed	Follow-up
Langer et al. 2009 ¹²⁷ Patient 11	54	Moderate	44	NR	NA	Hypoechoic mass (tail)	Hypoechoic mass (tail)	NA	Focal fibrosis PanIN1 + PanIN2	Distal pancreatectomy (spleen preserv)	No pathologies
Langer et al. 2009 ¹²⁷ Patient 12	42	Moderate	15	NR	NA	Cystic lesion (body)	Cystic lesion (body)	NA	Serous oligocystic adenoma	Distal pancreatectomy (spleen preserv)	No pathologies
Langer et al. 2009 ¹²⁷ Patient 13	54	High	12	NR	NA	Negative	Hypoechoic mass (tail)	NA	Lobular fibrosis with PanIN1 + squms metaplasia	Distal pancreatectomy + splenectomy	No pathologies
Langer et al. 2009 ¹²⁷ Patient 14	53	Moderate	5	NR	NA	Hypoechoic mass (tail)	Hypoechoic mass (tail)	NA	Lobular fibrosis with PanIN1 + IPMN gastric type	Distal pancreatectomy (spleen preserv)	NIDDM
Study averages for Langer et al. Patients 1–14 (above), patient follow-up = 44 Months	–	–	–	–	–	–	–	–	–	–	–

Table C-30. Screening studies: individual patient data for patients whose final diagnosis was based on surgery and/or biopsy (continued)

Study	Patient Age	Patient Risk	Patient Follow-	# Year Lesion Found	CT Dx	MRI/MRCP Dx	EUS Dx	ERCP Dx	Final Pathology Dx	Final Procedure Performed	Follow-up
Vasen et al. 2011 ¹²⁸ Patient 1	62	NR	NR	1	NR	5 mm tumor head-body	NR	NA	Well diff adenocarc	Pancreaticoduodenectomy	Alive 22 mos after dx
Vasen et al. 2011 ¹²⁸ Patient 2	49	NR	NR	1	NR	25 mm tumor tail	NR	NA	Mod diff adenocarcinoma	Distal pancreatectomy	Alive 17m after dx
Vasen et al. 2011 ¹²⁸ Patient 3	57	NR	NR	1 (overlooked at year 1, but visible in retrospect)	NR	10 mm tumor tail	NR	NA	Liver bx, poorly differentiated adenocarc	None- chemo – liver mets	Died from PC after 15 mo
Vasen et al. 2011 ¹²⁸ Patient 4	55	NR	24	3	NR	12 mm tumor tail	NR	NA	Mod diff adenocarcinoma	Distal pancreatectomy	Died from pc after 22 mo
Vasen et al. 2011 ¹²⁸ Patient 5	57	NR	28	2	NR	40 mm tumor tail	NR	NA	Mod diff adenocarcinoma	Distal pancreatectomy	Died after 22 mos
Vasen et al. 2011 ¹²⁸ Patient 6	70	NR	12	2	NR	20 mm tumor head-body	NR	NA	Mod diff adenocarcinoma	Resection pancreatic body and hemicolectomy	Died from pc and met carcin after 5 mo
Vasen et al. 2011 ¹²⁸ Patient 7	55	NR	29	4	NR	10 mm tumor body	NR	NA	None – melanoma mets	No surgery, melanoma mets	Died from melanoma mets 12 mo
Study averages for Vasen et al. Patients 1–7 (above), patient follow-up = 48 Months	–	–	–	–	–	–	–	–	–	–	–
Canto et al. 2006 ^{129,130} Patient 1	47	PJS personal and family hx	NR	1	Cystic lesion at uncinate process	NR	Cystic lesion at uncinate process	NR	IPMN w carcinoma in situ	Pancreatico-duodenectomy	NR

Table C-30. Screening studies: individual patient data for patients whose final diagnosis was based on surgery and/or biopsy (continued)

Study	Patient Age	Patient Risk	Patient Follow-	# Year Lesion Found	CT Dx	MRI/MRCP Dx	EUS Dx	ERCP Dx	Final Pathology Dx	Final Procedure Performed	Follow-up
Canto et al. 2006 ^{129,130} Patient 2	NR	3 FDR	NR	1	Mult cysts in tail	NR	Lesion and dilated main duct w 2 small cysts	NR	BD-IPMN, PanIN-3 with poss microinvasive adenoca	Distal pancreatectomy	NR
Canto et al. 2006 ^{129,130} Patient 3	75	3 relatives	NR	1	IPMN	NR	Chronic pancr, 2 cystic lesions, MD dilation at head and body	Chronic pancr, 2 cystic lesions, MD dilation at head and body	Diffuse chronic pancreatitis, mult PanIN (1/2)	Pancreatico-duodenectomy	NR
Canto et al. 2006 ^{129,130} Patient 4	40	4 relatives NIDDM	NR	1	???	NR	Nodule in tail, mild pancreatitis	NR	Chronic pancreatitis, PanIN1-2	Distal pancreatectomy	NR
Canto et al. 2006 ^{129,130} Patient 5		3 relatives	NR	2	Enlarge-ment and changes in morphol-ogy of pancreatic head, IPMN, FNA mucinous duct epithelium	NR	Enlargement and changes in morphology of pancreatic head, IPMN, FNA mucinous duct epithelium	NR	2 benign BD-IPMN adenoma, chronic pancreatitis	Pancreatico-duodenectomy	NR
Canto et al. 2006 ^{129,130} Patient 6	NR	3 relatives	NR	2	Normal	NR	Focal panc duct dilation, at 1 year bd-IPMN, dilated main PD communicating cystic mass	Focal panc duct dilation, at 1 year bd-IPMN, dilated main PD communi-cating cystic mass	IPMN-adenoma, mild focal fibrosis, focal PanIN-1	Pancreatico-duodenectomy	NR

Table C-30. Screening studies: individual patient data for patients whose final diagnosis was based on surgery and/or biopsy (continued)

Study	Patient Age	Patient Risk	Patient Follow-	# Year Lesion Found	CT Dx	MRI/MRCP Dx	EUS Dx	ERCP Dx	Final Pathology Dx	Final Procedure Performed	Follow-up
Canto et al. 2006 ^{129,130} Patient 7	76	5 relatives, BRCA2 mut, breast ca	NR	2	Normal pancreas initially, but ovarian mass; f/u CT cyst pancr duct uncinata	NR	Cyst communicating w panc duct in uncinata proc	NR	Adenocarcinoma	None	NR
Canto et al. 2006 ^{129,130} Patient 8	NR	2 FDR, 2 SDR	NR	2	Normal	NR	6 mm cyst head of pancr	NR	IPMN-adenoma, mult PanIN1-3	Pancreatico-duodenectomy	NR
Study averages for Canto et al. Patients 1–8 (above), patient follow-up = NR	–	–	–	–	–	–	–	–	–	–	–

Appendix D. Analyses and Risk of Bias Assessments

Analyses of Comparative Accuracy

Table D-1. Summary of analyses of comparative accuracy

Comparison	Clinical Decision	# Studies	Measure	Test 1 Estimate and 95% CI ^a	Test 2 Estimate and 95% CI ^a	Logit Difference and 95% CI ^b	Statistically Significantly Different?	Precise Enough to Indicate Approximately Equivalent Accuracy?
MDCT angiography without 3D reconstruction vs. with 3D reconstruction	Resectability in those not staged	1	Sensitivity	89% (95% CI: 68% to 97%)	100% (95% CI: 83% to 100%)	-1.5 (-4.3 to 1.2)	No	NA
MDCT angiography without 3D reconstruction vs. with 3D reconstruction	Resectability in those not staged	1	Specificity	79% (95% CI: 64% to 89%)	100% (95% CI: 91% to 100%)	-3 (-5.5 to -0.5)	Yes	See above cell
MDCT vs. EUS-FNA	Diagnosis	3	Sensitivity	87% (95% CI: 82% to 91%)	89% (95% CI: 85% to 93%)	-0.2 (-0.8 to 0.4)	No	No
MDCT vs. EUS-FNA	Diagnosis	3	Specificity	67% (95% CI: 53% to 78%)	81% (95% CI: 68% to 90%)	-0.7 (-1.7 to 0.2)	No	See above cell
MDCT vs. MRI	Diagnosis	7	Sensitivity	89% (95% CI: 82% to 94%)	89% (95% CI: 81% to 94%)	-0.01 (-1.4 to 1.5)	No	Yes
MDCT vs. MRI	Diagnosis	7	Specificity	90% (95% CI: 80% to 95%)	89% (95% CI: 74% to 95%)	0.1 (-2.5 to 2.8)	No	See above cell
MDCT vs. PET/CT	Diagnosis	6	Sensitivity	85% (95% CI: 80% to 90%)	91% (95% CI: 85% to 94%)	-0.6 (-1.2 to 0.1)	No	NA
MDCT vs. PET/CT	Diagnosis	6	Specificity	55% (95% CI: 44% to 66%)	72% (95% CI: 61% to 81%)	-0.7 (-1.4 to -0.1)	Yes	See above cell
EUS-FNA vs. PET/CT	Diagnosis	1	Sensitivity	81% (95% CI: 62% to 91%)	89% (95% CI: 72% to 96%)	-0.6 (-2.1 to 0.8)	No	No

Table D-1. Summary of analyses of comparative accuracy (continued)

Comparison	Clinical Decision	# Studies	Measure	Test 1 Estimate and 95% CI ^a	Test 2 Estimate and 95% CI ^a	Logit Difference and 95% CI ^b	Statistically Significantly Different?	Precise Enough to Indicate Approximately Equivalent Accuracy?
EUS-FNA vs. PET/CT	Diagnosis	1	Specificity	84% (95% CI: 62% to 94%)	74% (95% CI: 51% to 88%)	0.6 (-0.9 to 2.2)	No	See above cell
MRI vs. PET/CT	Diagnosis	1	Sensitivity	85% (95% CI: 64% to 95%)	85% (95% CI: 64% to 95%)	0 (-1.6 to 1.6)	No	No
MRI vs. PET/CT	Diagnosis	1	Specificity	72% (95% CI: 49% to 87%)	94% (95% CI: 74% to 99%)	-1.9 (-3.8 to 0.1)	No	See above cell
MDCT vs. EUS-FNA	Resectability in those not staged	1	Sensitivity	64% (95% CI: 46% to 79%)	68% (95% CI: 49% to 82%)	-0.2 (-1.2 to 0.9)	No	Yes
MDCT vs. EUS-FNA	Resectability in those not staged	1	Specificity	92% (95% CI: 75% to 98%)	88% (95% CI: 70% to 96%)	0.4 (-1.3 to 2.2)	No	See above cell
MDCT vs. MRI	Resectability in those not staged	2	Sensitivity	68% (95% CI: 47% to 85%)	52% (95% CI: 31% to 72%)	0.7 (-0.6 to 1.9)	No	No
MDCT vs. MRI	Resectability in those not staged	2	Specificity	89% (95% CI: 77% to 96%)	91% (95% CI: 80% to 97%)	-0.2 (-1.7 to 1.2)	No	See above cell
MDCT vs. EUS-FNA	T staging	1	T staging	Accurate T stage in 41% (95% CI: 20/49); overstaged T in 14% (95% CI: 7/49), understaged T in 44% (95% CI: 22/49)	Accurate T stage in 67% (95% CI: 33/49); overstaged T in 18% (95% CI: 9/49), understaged T in 14% (95% CI: 7/49)	RR 0.61 (0.41 to 0.90)	Yes	NA
MDCT vs. EUS-FNA	Vessel involvement	1	Sensitivity	56% (95% CI: 34% to 75%)	61% (95% CI: 39% to 80%)	-0.2 (-1.5 to 1)	No	No
MDCT vs. EUS-FNA	Vessel involvement	1	Specificity	94% (95% CI: 80% to 98%)	91% (95% CI: 76% to 97%)	0.4 (-1.3 to 2.1)	No	See above cell

Table D-1. Summary of analyses of comparative accuracy (continued)

Comparison	Clinical Decision	# Studies	Measure	Test 1 Estimate and 95% CI ^a	Test 2 Estimate and 95% CI ^a	Logit Difference and 95% CI ^b	Statistically Significantly Different?	Precise Enough to Indicate Approximately Equivalent Accuracy?
MDCT vs. MRI	T staging	1	T staging	Accurate T stage in 73% (95% CI: CI 62% to 84%), overstaging in 2% (95% CI: CI 0%-6%), and understaging in 25% (95% CI: CI 14%-36%).	Accurate T stage in 62% (95% CI: CI 49% to 75%), overstaging in 6% (95% CI: CI 0%-12%), and understaging in 32% (95% CI: CI 19%-45%).	RR 1.17 (0.90 to 1.52)	No	No
MDCT vs. MRI	N staging	1	Sensitivity	38% (95% CI: 21% to 57%)	15% (95% CI: 5% to 36%)	1.2 (-0.2 to 2.6)	No	No
MDCT vs. MRI	N staging	1	Specificity	79% (95% CI: 63% to 90%)	93% (95% CI: 78% to 98%)	-1.3 (-2.8 to 0.2)	No	See above cell
MDCT vs. MRI	Metastases	5	Sensitivity	48% (95% CI: 31% to 66%)	50% (95% CI: 19% to 82%)	-0.09 (-1.2 to 1.0)	No	No
MDCT vs. MRI	Metastases	5	Specificity	90% (95% CI: 81% to 95%)	95% (95% CI: 91% to 98%)	-0.9 (-2.2 to 0.9)	No	See above cell
MDCT vs. MRI	Precise stage	1	Precise stage	Accurate TNM stage in 46% (95% CI: CI 33% to 59%), overstaging in 8% (95% CI: CI 1%-15%), and understaging in 46% (95% CI: CI 33%-59%).	Accurate TNM stage in 36% (95% CI: CI 23% to 49%), overstaging in 7% (95% CI: CI 0%-14%), and understaging in 57% (95% CI: CI 44%-70%).	RR 1.28 (0.81 to 2.01)	No	No
MDCT vs. MRI	Vessel involvement	2	Sensitivity	68% (95% CI: 55% to 79%)	62% (95% CI: 48% to 74%)	0.3 (-0.5 to 1.1)	No	Yes
MDCT vs. MRI	Vessel involvement	2	Specificity	97% (95% CI: 94% to 98%)	96% (95% CI: 93% to 98%)	0.3 (-0.6 to 1.2)	No	See above cell
MDCT vs. MRI	Resectability in those staged	1	Sensitivity	67% (95% CI: 48% to 81%)	57% (95% CI: 37% to 74%)	0.4 (-0.7 to 1.5)	No	No

Table D-1. Summary of analyses of comparative accuracy (continued)

Comparison	Clinical Decision	# Studies	Measure	Test 1 Estimate and 95% CI ^a	Test 2 Estimate and 95% CI ^a	Logit Difference and 95% CI ^b	Statistically Significantly Different?	Precise Enough to Indicate Approximately Equivalent Accuracy?
MDCT vs. MRI	Resectability in those staged	1	Specificity	97% (95% CI: 84% to 99%)	90% (95% CI: 74% to 96%)	1.2 (-0.8 to 3.2)	No	See above cell
MDCT vs. PET/CT	N staging	1	Sensitivity	26% (95% CI: 14% to 43%)	32% (95% CI: 19% to 50%)	-0.3 (-1.4 to 0.8)	No	Yes
MDCT vs. PET/CT	N staging	1	Specificity	75% (95% CI: 50% to 90%)	75% (95% CI: 50% to 90%)	0 (-1.5 to 1.5)	No	See above cell
MDCT vs. PET/CT	Metastases	2	Sensitivity	57% (95% CI: 37% to 75%)	67% (95% CI: 47% to 83%)	-0.4 (-1.6 to 0.8)	No	NA
MDCT vs. PET/CT	Metastases	2	Specificity	91% (95% CI: 81% to 97%)	100% (95% CI: 95% to 100%)	-2.3 (-4.5 to -0.1)	Yes	See above cell
EUS-FNA vs. MRI	Precise stage	1	Precise stage	Accurate stage for 34/48 patients who had undergone surgical exploration. Of the 34, 34 were stage 2 and below, and 0 was stage 3 or above. The test understaged 13/48, and overstaged 1/48.	Accurate stage for 36/48 patients who had undergone surgical exploration. Of the 36, 35 were stage 2 and below, and 1 was stage 3 or above. The test understaged 12/48, and overstaged 0/48.	RR 0.94 (0.74 to 1.21)	No	Yes
MRI vs. PET/CT	Metastases	1	Sensitivity	57% (95% CI: 25% to 84%)	86% (95% CI: 48% to 97%)	-1.5 (-3.7 to 0.7)	No	No
MRI vs. PET/CT	Metastases	1	Specificity	86% (95% CI: 48% to 97%)	94% (95% CI: 64% to 100%)	-0.9 (-4 to 2.2)	No	See above cell

^a If multiple studies, this is the random-effects summary estimate, but if only one study, this is the single-study estimate

^b For most rows, this column indicates the results of statistical comparison of the two tests using equation 39 of Trikalinos.¹⁷ A positive logit difference favors test 1, and a negative logit difference favors test 2. For rows with RR (relative risk), it is the results of the statistical comparison of the two rates using relative risk; RR>1 favors test 1 and RR<1 favors test 2.

NA=Not applicable since the question of equivalence does not apply when a statistically significant difference exists for either sensitivity or specificity; RR=relative risk

Quality of Systematic Reviews

Modified AMSTAR Instrument^{131,132} for Systematic Reviews

The eight items in boldface below were required to be answered “Yes” in order for a systematic review to be considered high quality. Otherwise, the review was rated not high quality.

1. Was an *a priori* design or protocol provided?
- 2. Was a comprehensive search strategy performed?**
- 2a. Was this strategy appropriate to address the relevant Key Question of the CER?**
3. Was a list of included and excluded studies provided?
- 4. Was the application of inclusion/exclusion criteria unbiased?**
- 4a. Are the inclusion/exclusion criteria appropriate to address the relevant Key Question of the CER?**
5. Was there duplicate study selection and data extraction?
6. Were the characteristics of the included studies provided?
- 7. Was the individual study quality assessed?**
- 7a. Was the method of study quality assessment consistent with that recommended by the Methods Guide?**
- 7b. Was the scientific quality of the individual studies used appropriately in formulating conclusions?
- 8. Were the methods used to combine the findings of studies appropriate?**
9. Was the likelihood of publication bias assessed?
- 10. Have the authors disclosed conflicts of interest?**

Table D-2. Quality assessments of systematic reviews

Study	1	2	2a	3	4	4a	5 Sel.	5 Ext.	6	7	7a	7b	8	9	10	Meets Eight Most Important Criteria (High Quality)
Affolter et al. 2013 ¹	No	Yes	No	No	No	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes	No
Chen et al. 2013 ²	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Hébert-Magee et al. 2013 ³	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
Li et al. 2013 ¹⁴	No	No	Yes	No	Yes	Yes	No	Yes	Yes	No	No	No	Yes	No	Yes	No
Madhoun et al. 2013 ⁴	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes
Wang et al. 2013 ⁵	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	No
Puli et al. 2013 ⁶	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No
Chen et al. 2012 ⁷	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Hewitt et al. 2012 ⁸	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Wu et al. 2012 ⁹	No	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No	Yes	No	Yes	No
Wu et al. 2012 ¹⁰	No	No	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Yes	No
Tang et al. 2009 ¹¹	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No
Zhao et al. 2009 ¹⁵	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No
Hartwig et al. 2008 ¹²	No	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Bipat et al. 2005 ¹³	No	No	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No

Quality criteria: 1–A priori design or protocol provided, 2–Comprehensive search performed, 2a–Search strategy appropriate to address key questions of this review, 3–Lists of both included and excluded studies provided, 4–Inclusion/exclusion criteria applied in an unbiased manner, 4a–Inclusion/exclusion criteria appropriate to address key questions of this review, 5 sel.–Study selection done in duplicate, 5 ext.–Data abstraction done in duplicate, 6–Characteristics of individual studies reported in evidence table, 7–Quality of each individual study assessed, 7a–Quality assessment consistent with that recommended by the Methods Guide, 7b–Quality of the individual studies used appropriately in formulating conclusions, 8–Data synthesis methods appropriate, 9–The likelihood of publication bias assessed in a qualitative or quantitative manner, 10–Conflicts of interest disclosed by authors. Questions 2, 2a, 4, 4a, 7, 7a, 8, and 10 were deemed “most important.”

Risk of Bias of Comparative Accuracy Studies

1. Did the study enroll all, consecutive, or a random sample of patients?
2. **Was the study unaffected by spectrum bias (e.g., patients with known status before the study, or patients selected for being difficult to diagnose/stage)?**
3. Was prior experience with the test (technicians, readers) similar for the two imaging tests being compared in the study?
4. **Were the imaging tests performed within one month of each other (to avoid the possibility that the patient's true condition changed between tests)?**
5. **Was knowledge of the other test complementary (either both tests were read with knowledge of the other results, or neither test was read with knowledge of the other)?**
6. **Did the interpreters have the same other information available at the time of interpretation for the two imaging tests (other clinical information, 3rd test results)?**
7. **Was each test's accuracy measuring using the same reference standard (or a similar proportion of patients who underwent different reference standards such as clinical follow-up and surgical findings)?**
8. **Were readers of both tests of interest blinded to the results of the reference standard (or the reference standard was unknowable until after the tests were read)?**
9. Were the people determining the reference standard unaware of the diagnostic test results?

We defined LOW risk of bias as a study that has a YES for the six boldfaced items above (#2, and #4-#8). We defined HIGH risk of bias as a study that has a NO (or Not Reported) for these six items. We defined MEDIUM risk of bias a study that meets neither the LOW nor the HIGH criteria.

Table D-3. Risk of bias assessments of comparative accuracy studies

Study	1	2	3	4	5	6	7	8	9	Comments	Risk of Bias
Fang et al. 2012 ¹⁶	NR	Y	NR	Y	Y	Y	Y	Y	Y	–	Low
Herrmann et al. 2012 ¹⁷	NR	Y	Y	N	Y	Y	Y	Y	NR	–	Moderate
Tellez-Avila et al. 2012 ¹⁸	NR	Y	Y	NR	NR	NR	Y	Y	Y	Review of data obtained prospectively - EUS and CT - of pancreas lesion that then went to OR for surgical resection with goal of study being detection of vascular invasion, i.e., status of resectability. Not clearly stated but probably results of all tests to date available to all readers.	Moderate
Holzapfel et al. 2011 ¹⁹	Y	Y	NR	Y	Y	Y	Y	Y	NR	Two radiologists looked at each images together and came to consensus. Analysis of MDCT and MRI images were spaced 4 weeks apart to avoid any learning bias	Low
Koelblinger et al. 2011 ²⁰	Y	Y	Y	Y	Y	Y	Y	Y	NR	Reading sessions for CT and MR were separated by at least 8 weeks to minimize recall bias, and images were presented to readers in a different randomized order	Low
Motosugi et al. 2011 ²¹	NR	Y	N	Y	Y	Y	Y	Y	Y	–	Low
Rao et al. 2011 ²²	NR	N	Y	NR	Y	Y	Y	Y	NR	Bias against MRI because patients only had MRI if their case was more difficult (see Discussion section of the article). Small tumors only, which are harder to detect, thus possible spectrum bias.	Moderate
Shami et al. 2011 ²³	NR	Y	NR	NR	NR	NR	Y	Y	NR	Radiologists for MRI were blinded to EUS result, but did not report the order of the tests or whether EUS readers were blind to MRI result	Moderate
Takakura et al. 2011 ²⁴	NR	Y	Y	N	Y	Y	Y	Y	Y	Has flowchart for included patients, but doesn't say consecutive or all	Low
Imai et al. 2010 ²⁵	NR	N	NR	NR	Y	Y	Y	Y	NR	Possible spectrum bias because authors imaged for the presence of a particular kind of mets that is hard to detect (para-aortic lymph node metastasis or PALN)	Moderate
Lee et al. 2010 ²⁶	Y	Y	Y	Y	Y	Y	Y	Y	NR	The interval between reads was 2 weeks to minimize learning bias.	Low
Kauhanen et al. 2009 ²⁷	Y	Y	NR	Y	Y	Y	Y	Y	NR	–	Low
Farma et al. 2008 ²⁸	NR	Y	NR	NR	NR	NR	Y	NR	Y	All patients had a peroperative biopsy performed by percutaneous or endoscopi means. Clinical, radiographic, and pathologic follw-up was evaluated for each patient	Moderate

Table D-3. Risk of bias assessments of comparative accuracy studies (continued)

Study	1	2	3	4	5	6	7	8	9	Comments	Risk of Bias
Saif et al. 2008 ²⁹	NR	Y	NR	Y	Y	Y	Y	Y	NR	–	Low
Schick et al. 2008 ³⁰	Y	Y	NR	Y	NR	NR	Y	Y	NR	–	Moderate
Casneuf et al. 2007 ³¹	Y	Y	NR	NR	N	Y	Y	Y	Y	One reader for MDCT, and two readers together for PET/CT (one of whom had read the MDCT image at least 2 months earlier, and one who had read the PET alone image 2 at least months earlier). For PET/CT they had to come to consensus. This design is a bias in favor of PET/CT because there were always 4 eyes on the PET/CT, whereas CT only had 2 eyes. In addition, the PET/CT assessment was probably influenced (improved?) by the two readers' prior memory of the two individual scans.	Moderate
Tamm et al. 2007 ³²	NR	Y	NR	NR	N	N	Y	Y	N	MDCT images were read without knowledge of clinical, pathologic, or surgical data, or EUS-FNA findings. EUS-FNA was performed with knowledge of the MDCT finding. Also the reference standard for some patients was determined by the FNA. This design is a bias in favor of EUS-FNA.	Moderate
Mehmet Ertuk et al. 2006 ³³	Y	N	NR	Y	Y	Y	Y	Y	Y	Patient statuses were all known beforehand, hence probably spectrum bias. MDCT was always read first. The interval between reads was 4 weeks to minimize learning bias.	Moderate
Heinrich et al. 2005 ³⁴	NR	Y	NR	Y	NR	NR	Y	NR	NR	Findings on PET/CT were compared with results of standard staging and validated by intraoperative findings and histology of the resected specimen or biopsies. For patients who were diagnosed to have benign pancreatic lesion by PET/CT and did not undergo resection, long-term outcome was assessed to confirm the diagnosis made by PET/CT	Moderate
Agarwal et al. 2004 ³⁵	Y	Y	NR	NR	NR	Y	Y	Y	Y	–	Moderate
DeWitt et al. 2004 ³⁶	NR	Y	Y	Y	Y	Y	Y	Y	N	Readers for neither test were blind to previous radiographic data. Readers of the 2nd test (which was always MDCT) were blind to results from the 1st (which was always EUS-FNA)	Low
Lemke et al. 2004 ³⁷	NR	Y	NR	Y	N	NR	Y	NR	NR	2 radiologists evaluated the original CT and PET images as well as the fused images in a randomized order in 3 different settings with an interval of 2 weeks each, using a standardized questionnaire.	Moderate
Soriano et al. 2004 ³⁸	Y	Y	NR	NR	Y	Y	Y	Y	Y	Surgeons only saw a combined report of all the imaging tests, and did not know individual imaging results	Moderate

Table D-3. Risk of bias assessments of comparative accuracy studies (continued)

Study	1	2	3	4	5	6	7	8	9	Comments	Risk of Bias
Rieber et al. 2000 ³⁹	NR	Y	NR	NR	N	Y	Y	Y	NR	Readers: 3 different radiologists blinded to all clinical data regarding the patient.	Moderate

Appendix E. Sensitivity Analyses for Meta-Analyses Involving Multiple Readers per Study

Some comparative accuracy studies reported data separately for different readers. Our primary analyses discussed in the main report only used data from reader 1 for each such study. This appendix contains the results of sensitivity analysis of this choice, for two meta-analyses:

- MDCT versus MRI for diagnosis (a seven-study meta-analysis in which four of the seven studies reported multiple readers separately). Of the four studies, two reported three readers each, and two reported two readers each. Thus, we performed 35 sensitivity analyses ((2x3x2x3)-1 primary analysis).
- MDCT versus MRI for assessment of metastases (a five-study meta-analysis in which one of the five studies reported three readers separately. Thus, we performed 2 sensitivity analyses (3-1 primary analysis).

Sensitivity Analysis of MDCT vs. MRI for Diagnosis

The primary analysis yielded estimates for MDCT of 89% for sensitivity and 90% for specificity, whereas the estimates for MRI were 89% for sensitivity and 89% for specificity. The table below lists the results of the 35 sensitivity analyses; all analysis provided estimates that were very similar to the primary analysis.

Table E-1. Sensitivity analysis of MDCT vs. MRI for diagnosis

Which Readers were Used for the Four Studies Reporting Multiple Readers Separately	MDCT Sensitivity	MDCT Specificity	MRI Sensitivity	MRI Specificity
1,1,1,1 (primary analysis)	89% (95% CI: 82% to 94%)	90% (95% CI: 80% to 95%)	89% (95% CI: 81% to 94%)	89% (95% CI: 74% to 95%)
1,1,1,2	89% (95% CI: 83% to 94%)	90% (95% CI: 81% to 95%)	89% (95% CI: 80% to 94%)	88% (95% CI: 75% to 94%)
1,1,1,3	89% (95% CI: 83% to 94%)	90% (95% CI: 81% to 95%)	89% (95% CI: 81% to 94%)	89% (95% CI: 74% to 95%)
1,1,2,1	No convergence	No convergence	88% (95% CI: 80% to 93%)	90% (95% CI: 75% to 96%)
1,1,2,2	No convergence	No convergence	88% (95% CI: 80% to 93%)	89% (95% CI: 75% to 95%)
1,1,2,3	No convergence	No convergence	88% (95% CI: 80% to 93%)	90% (95% CI: 75% to 96%)

Table E-1. Sensitivity analysis of MDCT vs. MRI for diagnosis, (continued)

Which Readers were Used for the Four Studies Reporting Multiple Readers Separately	MDCT Sensitivity	MDCT Specificity	MRI Sensitivity	MRI Specificity
1,2,1,1	90% (95% CI: 82% to 94%)	90% (95% CI: 80% to 95%)	90% (95% CI: 80% to 95%)	89% (95% CI: 75% to 95%)
1,2,1,2	90% (95% CI: 83% to 94%)	90% (95% CI: 81% to 95%)	90% (95% CI: 80% to 95%)	88% (95% CI: 75% to 94%)
1,2,1,3	90% (95% CI: 83% to 94%)	90% (95% CI: 81% to 95%)	90% (95% CI: 80% to 95%)	89% (95% CI: 75% to 95%)
1,2,2,1	89% (95% CI: 82% to 93%)	90% (95% CI: 80% to 95%)	89% (95% CI: 80% to 94%)	90% (95% CI: 75% to 96%)
1,2,2,2	89% (95% CI: 82% to 93%)	90% (95% CI: 81% to 95%)	89% (95% CI: 79% to 94%)	89% (95% CI: 75% to 95%)
1,2,2,3	89% (95% CI: 82% to 93%)	90% (95% CI: 81% to 95%)	89% (95% CI: 80% to 94%)	90% (95% CI: 75% to 96%)
1,3,1,1	90% (95% CI: 82% to 94%)	90% (95% CI: 80% to 95%)	90% (95% CI: 80% to 95%)	89% (95% CI: 75% to 95%)
1,3,1,2	90% (95% CI: 83% to 94%)	90% (95% CI: 81% to 95%)	90% (95% CI: 80% to 95%)	88% (95% CI: 75% to 94%)
1,3,1,3	90% (95% CI: 83% to 94%)	90% (95% CI: 81% to 95%)	90% (95% CI: 80% to 95%)	89% (95% CI: 75% to 95%)
1,3,2,1	89% (95% CI: 82% to 93%)	90% (95% CI: 80% to 95%)	89% (95% CI: 80% to 94%)	90% (95% CI: 75% to 96%)
1,3,2,2	89% (95% CI: 82% to 93%)	90% (95% CI: 81% to 95%)	89% (95% CI: 79% to 94%)	89% (95% CI: 75% to 95%)
1,3,2,3	89% (95% CI: 82% to 93%)	90% (95% CI: 81% to 95%)	89% (95% CI: 80% to 94%)	90% (95% CI: 75% to 96%)
2,1,1,1	91% (95% CI: 84% to 95%)	89% (95% CI: 80% to 95%)	91% (95% CI: 82% to 95%)	89% (95% CI: 77% to 95%)
2,1,1,2	91% (95% CI: 84% to 95%)	90% (95% CI: 81% to 95%)	90% (95% CI: 81% to 95%)	88% (95% CI: 78% to 94%)
2,1,1,3	91% (95% CI: 84% to 95%)	90% (95% CI: 81% to 95%)	91% (95% CI: 82% to 95%)	89% (95% CI: 77% to 95%)
2,1,2,1	90% (95% CI: 84% to 94%)	89% (95% CI: 79% to 94%)	90% (95% CI: 81% to 94%)	90% (95% CI: 78% to 96%)
2,1,2,2	No convergence	No convergence	89% (95% CI: 81% to 94%)	89% (95% CI: 78% to 95%)
2,1,2,3	No convergence	No convergence	90% (95% CI: 81% to 94%)	90% (95% CI: 78% to 96%)

Table E-1. Sensitivity analysis of MDCT vs. MRI for diagnosis, (continued)

Which Readers were Used for the Four Studies Reporting Multiple Readers Separately	MDCT Sensitivity	MDCT Specificity	MRI Sensitivity	MRI Specificity
2,2,1,1	92% (95% CI: 84% to 96%)	89% (95% CI: 80% to 95%)	92% (95% CI: 82% to 96%)	89% (95% CI: 78% to 95%)
2,2,1,2	92% (95% CI: 84% to 96%)	90% (95% CI: 81% to 95%)	91% (95% CI: 81% to 96%)	88% (95% CI: 78% to 94%)
2,2,1,3	92% (95% CI: 84% to 96%)	90% (95% CI: 81% to 95%)	92% (95% CI: 82% to 96%)	89% (95% CI: 78% to 95%)
2,2,2,1	90% (95% CI: 84% to 94%)	89% (95% CI: 80% to 94%)	90% (95% CI: 81% to 95%)	90% (95% CI: 78% to 96%)
2,2,2,2	90% (95% CI: 84% to 94%)	90% (95% CI: 80% to 95%)	90% (95% CI: 81% to 95%)	89% (95% CI: 78% to 95%)
2,2,2,3	90% (95% CI: 84% to 94%)	90% (95% CI: 80% to 95%)	90% (95% CI: 81% to 95%)	90% (95% CI: 78% to 96%)
2,3,1,1	92% (95% CI: 84% to 96%)	89% (95% CI: 80% to 95%)	92% (95% CI: 82% to 96%)	89% (95% CI: 78% to 95%)
2,3,1,2	92% (95% CI: 84% to 96%)	90% (95% CI: 81% to 95%)	91% (95% CI: 81% to 96%)	88% (95% CI: 78% to 94%)
2,3,1,3	92% (95% CI: 84% to 96%)	90% (95% CI: 81% to 95%)	92% (95% CI: 82% to 96%)	89% (95% CI: 78% to 95%)
2,3,2,1	90% (95% CI: 84% to 94%)	89% (95% CI: 80% to 94%)	90% (95% CI: 81% to 95%)	90% (95% CI: 78% to 96%)
2,3,2,2	90% (95% CI: 84% to 94%)	90% (95% CI: 80% to 95%)	90% (95% CI: 81% to 95%)	89% (95% CI: 78% to 95%)
2,3,2,3	90% (95% CI: 84% to 94%)	90% (95% CI: 80% to 95%)	90% (95% CI: 81% to 95%)	90% (95% CI: 78% to 96%)

Note: "No convergence" means that the metandi command in stata did not converge on estimates, even after increasing the number of integration points to the maximum of 15.

Sensitivity Analysis of MDCT vs. MRI for Assessment of Metastases

The primary analysis yielded estimates for MDCT of 48% for sensitivity and 90% for specificity, whereas the estimates for MRI were 50% for sensitivity and 95% for specificity. The table below lists the results of the two sensitivity analyses; both provided estimates that were very similar to the primary analysis.

Table E-2. Sensitivity analysis of MDCT vs. MRI for assessment of metastases

Which Reader was Used for the One Study Reporting Multiple Readers Separately	MDCT Sensitivity	MDCT Specificity	MRI Sensitivity	MRI Specificity
1 (primary analysis)	48% (95% CI: 31% to 66%)	90% (95% CI: 81% to 95%)	50% (95% CI: 19% to 81%)	95% (95% CI: 91% to 98%)
2	48% (95% CI: 31% to 65%)	91% (95% CI: 81% to 96%)	54% (95% CI: 18% to 86%)	96% (95% CI: 93% to 98%)
3	48% (95% CI: 31% to 65%)	91% (95% CI: 81% to 96%)	54% (95% CI: 18% to 86%)	96% (95% CI: 93% to 98%)

Sensitivity Analysis of MDCT vs. MRI for Assessment of Metastases

The primary analysis yielded estimates for MDCT of 48% for sensitivity and 90% for specificity, whereas the estimates for MRI were 50% for sensitivity and 95% for specificity. The table below lists the results of the two sensitivity analyses; both provided estimates that were very similar to the primary analysis.

Table E-3. Sensitivity analysis of MDCT vs. MRI for assessment of metastases

Which Reader was Used for the Two Study Reporting Multiple Readers Separately	MDCT Sensitivity	MDCT Specificity	MRI Sensitivity	MRI Specificity
1,1 (primary analysis)	48% (95% CI: 31% to 66%)	90% (95% CI: 81% to 95%)	50% (95% CI: 19% to 81%)	95% (95% CI: 91% to 98%)
2	48% (95% CI: 31% to 65%)	91% (95% CI: 81% to 96%)	54% (95% CI: 18% to 86%)	96% (95% CI: 93% to 98%)
3	48% (95% CI: 31% to 65%)	91% (95% CI: 81% to 96%)	54% (95% CI: 18% to 86%)	96% (95% CI: 93% to 98%)

Appendix F. Appendix References

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