

Draft Comparative Effectiveness Review

Number xx

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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To be added to final report.

Technical Expert Panel

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.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

To be added to final report

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Imaging Tests for the Diagnosis and Staging of Pancreatic Adenocarcinoma

Structured Abstract

Objectives. Synthesize the available information on using imaging for diagnosis, staging, and screening pancreatic adenocarcinoma cancer.

Data sources. We searched EMBASE, MEDLINE, PubMed, and The Cochrane Library for the period 1980 through May 2013 for published, English-language, full-length articles on using multidetector computed tomography (MDCT), endoscopic ultrasound with fine-needle aspiration (EUS-FNA), magnetic resonance imaging (MRI), and positron emission tomography–computed tomography (PET/CT) for screening, diagnosis, and staging pancreatic adenocarcinoma. The searches identified 8,834 citations; after screening against the inclusion criteria, we included 10 systematic reviews and 102 studies.

Methods. We extracted data from the included studies and constructed evidence tables. 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, or a conclusion of approximate equivalence, 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 tabled the important information and summarized the evidence qualitatively.

Results. We included 10 systematic reviews and 102 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. 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 sufficient evidence to conclude that PET/CT is more accurate than MDCT in assessing metastases. No included studies reported data on clinical management, survival, quality, or the impact of patient characteristics or tumor characteristics or operator experience on comparative accuracy. Many studies have reported procedural harms, but they are generally rare and are different for different imaging modalities. In the screening of people at high risk of developing pancreatic adenocarcinoma, most people have negative results on pertinent imaging tests, and available studies do not correlate the results of a given imaging test to subsequent diagnoses.

Conclusions. Many gaps remain in the comparative assessment of imaging tests for diagnosing and staging pancreatic adenocarcinoma. The prominent gaps involve minimal information on MDCT angiography, imprecision in existing data, a lack of comparative data on patient-oriented outcomes and factors that could influence comparative accuracy, and minimal data on screening accuracy for any given imaging test.

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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 45,000 people will receive a diagnosis of pancreatic cancer and 38,000 will die 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 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),⁵ and the median survival patients with unresectable tumors is only 6–10 months.⁶

For the patient, given the poor prognosis of most cases, the differences in modalities and the consequences of their use are important to understand. 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

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 assessing 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 superior mesenteric artery. 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. It provides three-dimensional multiplanar reconstruction images enabling determination of tumor size, extent, and spread, with a standardized pancreas protocol.^{8,9} 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 cancer risk. Other current 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).

Objectives of this Review

The primary objective of this review is to synthesize the available information on using imaging for diagnosis, staging and screening. 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 are listed below:

1. What is the comparative effectiveness of imaging techniques (e.g., MDCT angiography with or without three-dimensional (3D) reconstruction, other MDCT, 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 angiography with or without 3D reconstruction, other MDCT, 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 angiography with or without 3D reconstruction, other MDCT, 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 angiography with or without 3D reconstruction, other MDCT, 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) angiography with 3D reconstruction
- Other MDCT
- Endoscopic ultrasound with fine-needle aspiration (EUS-FNA)
- Magnetic resonance imaging (MRI)
- Positron emission tomography combined with computed tomography (PET/CT)

Reference Standards to Assess Test Performance

- Histopathological examination of tissue and/or biopsy
- Intra-operative findings

- Clinical followup

Comparators

- Any direct comparisons of the imaging tests of interest

Outcomes

- Test performance outcomes
 - 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 May 2013. The full search strategy is shown in Appendix A.

Literature screening 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 and exclusion criteria. Studies that appeared to meet the inclusion criteria were retrieved in full, and we screened them again, in duplicate, against the inclusion and exclusion 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.

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. 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.^{10,11} In addition, 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.¹²⁻¹⁶
- 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: Moher et al. (2000) have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn.¹⁷ 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.¹⁸ 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 key questions on single-test accuracy. For Key Questions 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)¹⁹ 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 section D on risk of bias.
- b. For any key questions 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 key questions 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 MDCT and 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 key questions 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 Key Question 3 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 Key Question 3b on patient perspectives of imaging tests, any study design was accepted.
- g. For Key Question 4 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 *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 (Key Question [KQ]1a 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 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 Key Question 3b on patient perspectives of imaging tests. We used a minimum of 50 patients for data on harms (KQ3) or screening (KQ4).
 - c. For all key questions, 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

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 abstracted included general study characteristics (e.g., country, setting, study design, enrolled N), 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 and independently assigned the review as either low risk of bias, or moderate/high risk of bias. Discrepancies in the category assignment were resolved by consensus. For studies comparing two or more tests, we used a set of nine risk-of-bias items after

considering the QUADAS-2,²⁰ as well as additional issues that specifically address bias in the comparison of diagnostic tests.

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).²¹ 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 rating of the strength of evidence: high, moderate, low, or insufficient. This rating is made separately for each outcome of each comparison of each key question.

The EPC system requires that reviewers select only the most important outcomes of a review 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 staging, N [nodal] staging, metastases, vessel involvement, and precise stage), resectability in staged patients, and clinical outcomes (clinical management, survival, and quality of life).

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 approximate equivalence. If none of these three conclusions were appropriate, we rated the evidence insufficient. If the evidence was sufficient to permit a conclusion, then the rating was high, moderate, or low. The rating was provided by two independent raters, and discrepancies were resolved by consensus. Below, we discuss the eight domains and how they were considered as inputs to the rating.

Applicability

The applicability of the evidence involves 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 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.

Data Analysis and Synthesis

For comparing imaging tests, we synthesized the evidence 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. 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 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-analysis²² of each test's accuracy data using the “metandi” command in STATA.²³ If this model could not be fit for a given test (i.e., if there were three or fewer studies in the analysis, or the model did not converge), we performed separate analyses of sensitivity and specificity using Meta-Disc (freeware developed by the Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain).²⁴ Using the meta-analytic results, we used equation 39 in Trikalinos et al. (2013)²⁵ 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 confidence interval around the difference was sufficiently narrow to permit a conclusion of approximate equivalence; disagreements were resolved by consensus.

Peer Review and Publication

Peer reviewers are 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 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

Evidence Base

The literature searches identified 8,834 citations, and after duplicate review, we excluded 8,189 of them. The most common reason for exclusion was that the article did not involve diagnosis, staging, screening, or harms. We retrieved the other 645 articles in full, and after duplicate review, we excluded 526 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 key questions. See Appendix B for a list of the publications excluded at the full article level. We included the remaining 119 publications, which described 112 unique studies/reviews (seven publications reported overlapping patients). Of the 112, 10 were systematic reviews and 102 were studies.

Key Question 1: What is the comparative effectiveness of imaging techniques (e.g., MDCT angiography with or without 3D reconstruction, other MDCT, EUS-FNA, PET/CT, MRI) for diagnosis of pancreatic adenocarcinoma in adults with suspicious symptoms?

Key Question 1a. What is the accuracy of each imaging technique for diagnosis and assessment of resectability?

Nine systematic reviews met the inclusion criteria for this question, of which three were both recent (published 2009 or later) and of high quality (meeting all eight of the quality criteria deemed most important).

For EUS-FNA in diagnosing pancreatic cancer, the three recent high-quality reviews²⁶⁻²⁸ 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,²⁹ which was deemed not of high quality and is outdated (2005). MRI was addressed in three reviews,²⁹⁻³¹ 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 two reviews,^{30,32} neither of which were high quality. The low quality of all the reviews on CT, MRI, and PET/CT limit the confidence one can have in the quantitative estimates of accuracy.

The only review that included resectability as an outcome was outdated, of low quality, and analyzed only CT and MRI studies. It found a statistically insignificant difference in sensitivity favoring MRI and a statistically insignificant difference in specificity favoring CT. Because of the low quality of the review and the large confidence intervals on the authors' summary estimates, we conclude that the evidence is inadequate to prove any difference in effectiveness between CT and MRI.

Key Question 1b. 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. Studies were 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 by seven studies. These studies found consistently high sensitivity (89 percent) and specificity (90 percent) for both imaging modalities.

All other subquestions for Key Question 1: No included studies reported pertinent data.

Conclusions for Key Question 1

Nine included systematic reviews yielded the following conclusions regarding single-test accuracy:

- 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 percent confidence interval [CI], 86 percent to 94 percent) and a specificity estimate of 85 percent (95 percent CI, 76 percent to 91 percent).

- 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.
- 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.
- 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.
- For MDCT, in assessing the resectability of tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 81 percent (95 percent CI, 76 percent to 85 percent) and a specificity estimate of 82 percent (95 percent CI, 77 percent to 97 percent).
- For MRI, in assessing the resectability of tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 82 percent (95 percent CI, 69 percent to 91 percent) and a specificity estimate of 78 percent (95 percent CI, 63 percent to 87 percent).

Eighteen included primary studies yielded the following conclusions regarding comparative test accuracy:

- MDCT and EUS-FNA are approximately equally accurate in the assessment of resectability of pancreatic adenocarcinoma in symptomatic adults with unstaged disease (Strength of evidence: low)
- MDCT and MRI are approximately equally accurate in the diagnosis of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate)

Key Question 2: What is the comparative effectiveness of imaging techniques (e.g., MDCT angiography with or without 3D reconstruction, other MDCT, EUS-FNA, PET/CT, MRI) for staging of pancreatic adenocarcinoma among adults with a diagnosis of pancreatic adenocarcinoma?

Key Question 2a. What is the staging accuracy of each imaging technique (for tumor size, lymph node status, vessel involvement, metastases, stage I–IV, and resectability)?

Only one systematic review²⁶ addressed this question. It was a low-quality review of CT studies that includes studies that used single-slice CT scanners. Rather than using the TNM (tumor, lymph node, distant metastases) system of staging, it examined only the question of whether the primary tumor had invaded surrounding vasculature. The authors reported summary results for all studies included and for a subset of studies published between 2004 and 2008, most of which used multi-slice CT. Sensitivity was considerably higher for the later studies than for the rest, with no corresponding loss of specificity. When the review considered only studies published since 2004, the review estimated the sensitivity and specificity of CT to be 85 percent (95 percent CI, 78 percent to 91 percent) and 82 percent (95 percent CI, 74 percent to 88 percent), respectively.

Key Question 2b. 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. Two 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 percent of patients were accurately T-staged by EUS-FNA as compared to only 41 percent by MDCT). Another conclusion, based on two studies, was the similarity in the accuracy of the assessment of vessel involvement by MDCT and MRI (sensitivities 62 percent to 68 percent, specificities 96 percent to 97 percent). The third conclusion, based on two studies, was that PET/CT is more accurate in the assessment of metastases than MDCT (67 percent vs. 57 percent for sensitivity, and 100 percent vs. 91 percent for specificity).

All other subquestions for Key Question 2: No included studies reported pertinent data.

Conclusions for Key Question 2

One included systematic review yielded the following conclusion about single-test accuracy:

- When the review considered only studies published since 2004, the review estimated the sensitivity and specificity of CT to be 85 percent (95 percent CI, 78 percent to 91 percent) and 82 percent (95 percent CI, 74 percent to 88 percent), respectively.

Twelve included primary studies yielded the following conclusions about comparative test accuracy:

- 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 are approximately equally accurate 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 metastases of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate)

Key Question 3: What are the rates of harms of imaging techniques (e.g., MDCT angiography with or without 3D reconstruction, other MDCT, EUS-FNA, PET/CT, MRI) when used to diagnose and/or stage pancreatic adenocarcinoma?

We included a total of 72 studies for this key question: 44 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

percent to 2.4 percent of patients), postprocedural pain (occurring in 0.1 percent to 2.0 percent of patients), and bleeding/puncture/perforation (occurring in 0 percent to 4.3 percent of patients).

Key Question 3a. How are patient factors related to the harms of different imaging techniques?

No included studies addressed this question.

Key Question 3b. 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.

Conclusions for Key Question 3

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 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/bleeding. Regarding patient tolerance, one study of screening found that about 10 percent of patients stated that EUS-FNA and MRI are very uncomfortable.

Key Question 4: What is the screening accuracy of imaging techniques (e.g., MDCT angiography with or without 3D reconstruction, other MDCT, 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)?

Conclusions for Key Question 4

Six included studies involved the screening of 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.
- The large majority of high-risk individuals (HRIs) who undergo screening for pancreatic adenocarcinoma either have completely normal imaging studies (52 percent to 63 percent) or have some abnormal imaging that was not sufficiently concerning to warrant biopsy or surgery (18 percent to 45 percent).
- Only 2 percent to 18 percent of HRIs screened received either a biopsy or surgery based on imaging findings (any imaging modality—MDCT, EUS with or without FNA, MRI), amounting to a total of 46 HRIs (7 percent) from the 6 studies.

Discussion

This comparative review summarizes evidence on imaging tests (MDCT angiography, other MDCT, 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, nor to demonstrate similar accuracy among tests. We conclude that MDCT and EUS-FNA have similar accuracy in the assessment of resectability in patients with unstaged disease, and that EUS-FNA has a slight advantage over MDCT with respect to T staging. Further, we concluded 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 than MDCT in the assessment of metastases.

No included studies compared these tests for their subsequent impacts on patient management, survival, or quality of life. Future comparative studies should measure these patient-oriented outcomes. Another 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 best, but for patients without jaundice that same test is worst), and tumor characteristics (e.g., for staging small tumors, one test is best, but for large tumors another test is best).

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 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/bleeding. Regarding patient tolerance, one study of screening found that about 10 percent of patients state that EUS-FNA and MRI are very uncomfortable.

For screening, most people at high risk of developing pancreatic adenocarcinoma have negative results on pertinent imaging tests. Available studies do not correlate the results of a given imaging test to subsequent diagnoses, therefore one cannot determine the screening accuracy of any given imaging test.

Executive Summary Reference List

1. American Cancer Society (ACS). Cancer facts & figures 2012. Atlanta (GA): American Cancer Society (ACS); 2012. 65 p. Also available: <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspsc-031941.pdf>.
2. Sharma C, Eltawil KM, Renfrew PD, et al. Advances in diagnosis, treatment and palliation of pancreatic carcinoma: 1990-2010. *World J Gastroenterol*. 2011 Feb 21;17(7):867-97. PMID: 21412497
3. Pancreatic cancer. [internet]. Bethesda (MD): National Cancer Institute (NCI); [accessed 2013 Mar 13]. [2 p]. Available: <http://www.cancer.gov/cancertopics/types/pancreatic>.
4. Dabizzi E, Assef MS, Raimondo M. Diagnostic management of pancreatic cancer. *Cancers*. 2011 Mar;3(1):494-509.
5. Pancreatic cancer treatment (PDQ). Health professional version. [internet]. Bethesda (MD): National Cancer Institute (NCI); 2012 Jul 17 [accessed 2012 Nov 8]. [27 p]. Available: <http://www.cancer.gov/cancertopics/pdq/treatment/pancreatic/HealthProfessional/page1/AllPages/Print>.
6. Benson AB III, Myerson RJ, Sasson AR. Pancreatic, neuroendocrine GI, and adrenal cancers. In: *Cancer management: a multidisciplinary approach*. 14th ed. [internet]. New York (NY): UBM Medica LLC; 2011 Oct 28 [accessed 2013 Feb 28]. Available: <http://www.cancernetwork.com/cancer-management/pancreatic/article/10165/1802606>.
7. Tamm EP, Balachandran A, Bhosale PR, et al. Imaging of pancreatic adenocarcinoma: update on staging/resectability. *Radiol Clin North Am*. 2012 May;50(3):407-28. PMID: 22560689
8. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol*. 2009 Jul;16(7):1727-33. PMID: 19396496
9. Wong JC, Lu DS. Staging of pancreatic adenocarcinoma by imaging studies. *Clin Gastroenterol Hepatol*. 2008 Dec;6(12):1301-8. PMID: 18948228
10. Chalmers I, Adams M, Dickersin K, et al. A cohort study of summary reports of controlled trials. *JAMA*. 1990 Mar 9;263(10):1401-5. PMID: 2304219
11. Neinstein LS. A review of Society for Adolescent Medicine abstracts and Journal of Adolescent Health Care articles. *J Adolesc Health Care*. 1987 Mar;8(2):198-203. PMID: 3818406
12. Dundar Y, Dodd S, Williamson P, et al. Case study of the comparison of data from conference abstracts and full-text articles in health technology assessment of rapidly evolving technologies: does it make a difference? *Int J Technol Assess Health Care*. 2006 Jul;22(3):288-94.
13. De Bellefeuille C, Morrison CA, Tannock IF. The fate of abstracts submitted to a cancer meeting: factors which influence presentation and subsequent publication. *Ann Oncol*. 1992 Mar;3(3):187-91. PMID: 1586615
14. Scherer RW, Langenberg P. Full publication of results initially presented in abstracts. In: *Cochrane Library [Cochrane methodology review]*. Issue 2. Oxford: Update Software; 2001 [accessed 2001 Apr 23]. [35 p]. Available: <http://www.cochrane.org/index.htm>.
15. Yentis SM, Campbell FA, Lerman J. Publication of abstracts presented at anaesthesia meetings. *Can J Anaesth*. 1993 Jul;40(7):632-4. PMID: 8403137

16. Marx WF, Cloft HJ, Do HM, et al. The fate of neuroradiologic abstracts presented at national meetings in 1993: rate of subsequent publication in peer-reviewed, indexed journals. *AJNR Am J Neuroradiol.* 1999 Jun-Jul;20(6):1173-7. PMID: 10445467
17. Moher D, Pham B, Klassen TP, et al. What contributions do languages other than English make on the results of meta-analyses? *J Clin Epidemiol.* 2000 Sep;53(9):964-72. PMID: 11004423
18. Juni P, Hoenstein F, Sterne J, et al. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. *Int J Epidemiol.* 2002 Feb;31(1):115-23. PMID: 11914306
19. White CM, Ip S, McPheeters M, et al. Using existing systematic reviews to replace de novo processes in conducting Comparative Effectiveness Reviews. In: *Methods guide for comparative effectiveness reviews.* Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2009 Sep. Also available: <http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60>. PMID: 21433402
20. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol.* 2003 Nov 10;3(1):25. Also available: <http://www.biomedcentral.com/content/pdf/1471-2288-3-25.pdf>. PMID: 14606960
21. Singh S, Chang S, Matchar DB, et al. Grading a body of evidence on diagnostic tests (AHRQ publication no. 12-EHC079-EF). In: *Methods guide for medical test reviews* (AHRQ publication no. 12-EHC017). Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2012 Jun 1. p. 7.1-15. Also available: <http://www.ncbi.nlm.nih.gov/books/NBK98248/#ch7.r11>.
22. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol.* 2005 Oct;58(10):982-90. PMID: 16168343
23. STATA statistics/data analysis. MP parallel edition. College Station (TX): StataCorp; 1984-2007. Single user Stata for Windows. Also available: <http://www.stata.com>.
24. Zamora J, Abraira V, Muriel A, et al. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol.* 2006;6:31. PMID: 16836745
25. Trikalinos TA, Hoaglin DC, Small KM, et al. Evaluating practices and developing tools for comparative effectiveness reviews of diagnostic test accuracy: methods for the joint meta-analysis of multiple tests. *Methods research report.* Contract no. 290-2007-10055-I. Rockville (MD): Agency for Healthcare Research and Quality; 2013 Jan. 49 p. (AHRQ publication no. 12(13)-EHC151-EF). Also available: http://effectivehealthcare.ahrq.gov/ehec/products/291/1380/Methods%20Report_Evaluating-Practices-Developing-Tools_Final_01-14-2013.pdf.
26. Madhoun MF, Wani SB, Rastogi A, et al. The diagnostic accuracy of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of solid pancreatic lesions: a meta-analysis. *Endoscopy.* 2013;45(2):86-92. PMID: 23307148
27. Chen J, Yang R, Lu Y, et al. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesion: a systematic review. *J Cancer Res Clin Oncol.* 2012 Sep;138(9):1433-41. PMID: 22752601
28. Hewitt MJ, McPhail MJW, Possamai L, et al. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: A meta-analysis. *Gastrointest Endosc.* 2012 Feb;75(2):319-31.

29. Bipat S, Phoa SS, 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):438-45. PMID: 16012297
30. Wu LM, Hu JN, Hua J, et al. Diagnostic value of diffusion-weighted magnetic resonance imaging compared with Fluorodeoxyglucose positron emission tomography/computed tomography for pancreatic malignancy: a meta-analysis using a hierarchical regression model. *J Gastroenterol Hepatol.* 2012 Jun;27(6):1027-35. PMID: 22414092
31. Wu LM, Xu JR, Hua J, et al. Value of diffusion-weighted imaging for the discrimination of pancreatic lesions: a meta-analysis. *Eur J Gastroenterol Hepatol.* 2012 Feb;24(2):134-42. PMID: 22241215
32. Tang S, Huang G, Liu J, et al. Usefulness of 18F-FDG PET, combined FDG-PET/CT and EUS in diagnosing primary pancreatic carcinoma: a meta-analysis. *Eur J Radiol.* 2011 Apr;78(1):142-50. PMID: 19854016

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 45,000 people will receive a diagnosis of pancreatic cancer and 38,000 will die 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.^{4,33} The most common type of pancreatic cancer is adenocarcinoma (approximately 90 percent 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.³³

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 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),⁵ and the median survival of patients with unresectable tumors is only 6–10 months.⁶

Common symptoms leading to suspicion of pancreatic cancer are jaundice, epigastric pain, and weight loss;³⁴ 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.³⁵ 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. 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:³⁶

- 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 may not be performed, and the disease is often staged at surgery. For unresectable cases, however, a biopsy is taken and a formal stage is determined to guide the planning of treatments such as chemotherapy.

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:³⁷

- 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.⁷

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.^{36,38} However, others believe that minor arterial involvement (stage III) may still permit resection.^{7,39} Vincent et al. (2011)³⁹ argued that some stage III cases are borderline resectable and may be appropriate targets for neoadjuvant therapy followed by resection.

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).⁴⁰ However, some recommend screening those who are at high risk of developing pancreatic cancer. One report⁴¹ 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.⁴¹

Imaging Technologies

Multidetector Computed Tomography

A multidetector computed tomography (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.^{8,9} 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 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 (ACR) offers a voluntary accreditation program for CT facilities.⁴²

One notable type of MDCT is MDCT with angiography with or without 3D reconstruction.⁴³ This technology permits more precise imaging of blood vessels than other forms of MDCT. Given its importance, in our review, we will separate it from other forms of MDCT.

The following sections describe other procedures and imaging tests to assist diagnosis and/or staging of pancreatic adenocarcinoma, including 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 of 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 the relative newness of some technologies (e.g., PET/CT).

Endoscopic Ultrasound with Fine-Needle Aspiration

For EUS-FNA, a specialized ultrasound probe is introduced orally and advanced via endoscope through the upper gastrointestinal tract toward the pancreas. The probe's proximity to the pancreas allows the ultrasound to access and image the entire pancreas, the related vasculature, and associated lymph nodes. 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).³⁷ Reported disadvantages of EUS-FNA include the procedure's invasiveness, dependence on the skill of the endoscopist, and inability to evaluate for distant metastases.⁹ 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. ACR 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.⁴⁴

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.⁹ MRI can also be used as an adjunct to CT to better detect extrahepatic disease.^{45,46} There is no nationwide compulsory accreditation for MRI facilities. ACR administers a voluntary accreditation program.⁴⁷

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 volume of clinical procedures.⁴⁸

Objectives of This Review

This review concerns imaging tests to identify and diagnose suspected pancreatic cancer and determine stage and surgical resectability of the disease.^{4,49} Pancreatic adenocarcinoma is fatal if untreated, so it is critical to choose the right imaging test and initiate therapy in a timely manner. A comparative effectiveness review (CER) on this topic can assist medical decisions in several ways. First, different imaging tests are believed to have utility in different circumstances (e.g., when suspicious of metastatic disease vs. localized disease) and a clear delineation of the relevant evidence would help guide clinicians and patients in choosing the most appropriate imaging test. 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 and 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 angiography with or without 3D reconstruction, other MDCT, 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 angiography with or without 3D reconstruction, other MDCT, 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 angiography with or without 3D reconstruction, other MDCT, 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 angiography with or without 3D reconstruction, other MDCT, 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

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. PICOTS for each key question

KQ	Population	Interventions	Comparators	Outcomes
1a	P1	MDCT angiography with or without 3D reconstruction, other MDCT, 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	One 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)

Table 1. PICOTS for each key question (continued)

KQ	Population	Interventions	Comparators	Outcomes
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
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	One 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	One 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

Table 1. PICOTS for each key question (continued)

KQ	Population	Interventions	Comparators	Outcomes
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

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. 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=combined position emission tomography and computed tomography; T=tumor stage

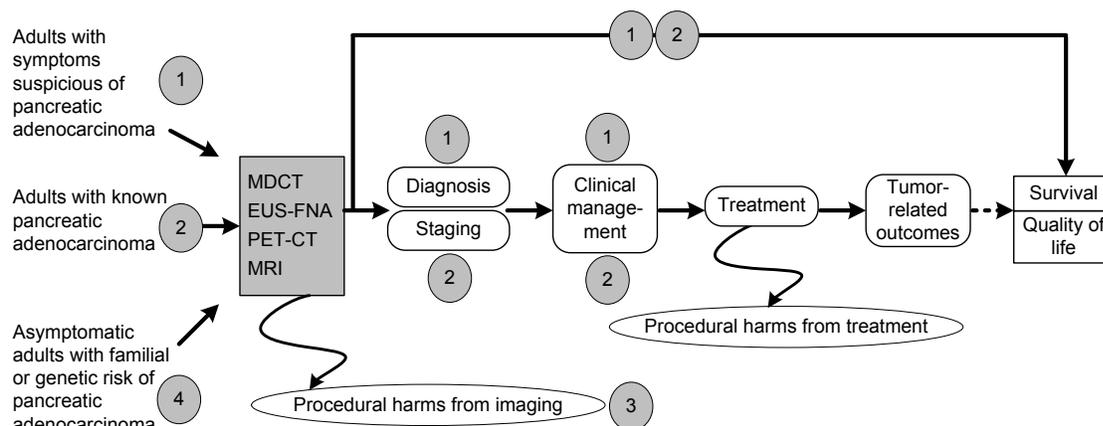
Conceptual Framework

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

Figure 1: 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 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

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 May 2013. The full search strategy is shown in Appendix A.

Literature screening 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 and exclusion criteria. Studies that appeared to meet the inclusion criteria were retrieved in full, and we screened them again, in duplicate, against the inclusion and exclusion 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.

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.^{10,11} In addition, 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.¹²⁻¹⁶
- 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.¹⁷ 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.¹⁸ 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. 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 key questions on single-test accuracy. For Key Questions 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)¹⁹ 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 section D on risk of bias.
- b. For any key questions 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 key questions 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 key questions 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 Key Question 3 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 Key Question 3b on patient perspectives of imaging tests, any study design was accepted.
- g. For Key Question 4 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 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 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.
 - 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 Key Question 3b on patient perspectives of

imaging tests. We used a minimum of 50 patients for data on harms (KQ3) or screening (KQ4).

- c. For all key questions, 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 N), 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, EPC guidance by White et al. (2009)¹⁹ 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 Table D-2 of Appendix D. For each included review, two analysts independently answered 15 items and independently assigned the review as either low risk of bias, or moderate/high risk of bias. Discrepancies in the category assignment were resolved by consensus. A review was considered low risk of bias if it met eight specific items (see Appendix D).

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 (see Table D-3 of Appendix D).

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).²¹ 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 rating of the strength of evidence: high, moderate, low, or insufficient. This rating is made separately for each outcome of each comparison of each key question. Definitions for these categories is provided in Table 2 below.

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, i.e., 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).²¹

The EPC system requires that reviewers select only 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.

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 require 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 approximate equivalence. If none of these three conclusions were appropriate, we rated the evidence insufficient. If the evidence was sufficient to permit a conclusion, then the rating was high, moderate, or low. The rating was provided by two independent raters, and discrepancies were resolved by consensus. Below, we discuss the eight domains and how they were considered:

Risk of bias (see the section Risk of Bias Evaluation above). 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 rating than a set of studies at moderate or high risk of bias.

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 approximate equivalence.

Publication 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 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 rating 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 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 described, and if data permitted, subgroups of studies by setting were analyzed separately.

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.²³ If this model could not be fit for a given test (i.e., if there were three 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).²⁴ Using the meta-analytic results, we used equation 39 in Trikalinos et al. (2013)²⁵ 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 approximate equivalence; 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.

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 the relative risk of accuracy staging, and compared imaging tests statistically using standard methods.

Peer Review and Publication

The review protocol was posted on August 9, 2013 at <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1620&pageaction=displayproduct>. 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 key question.

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; and Appendix D, Analyses and Risk of Bias Assessments.

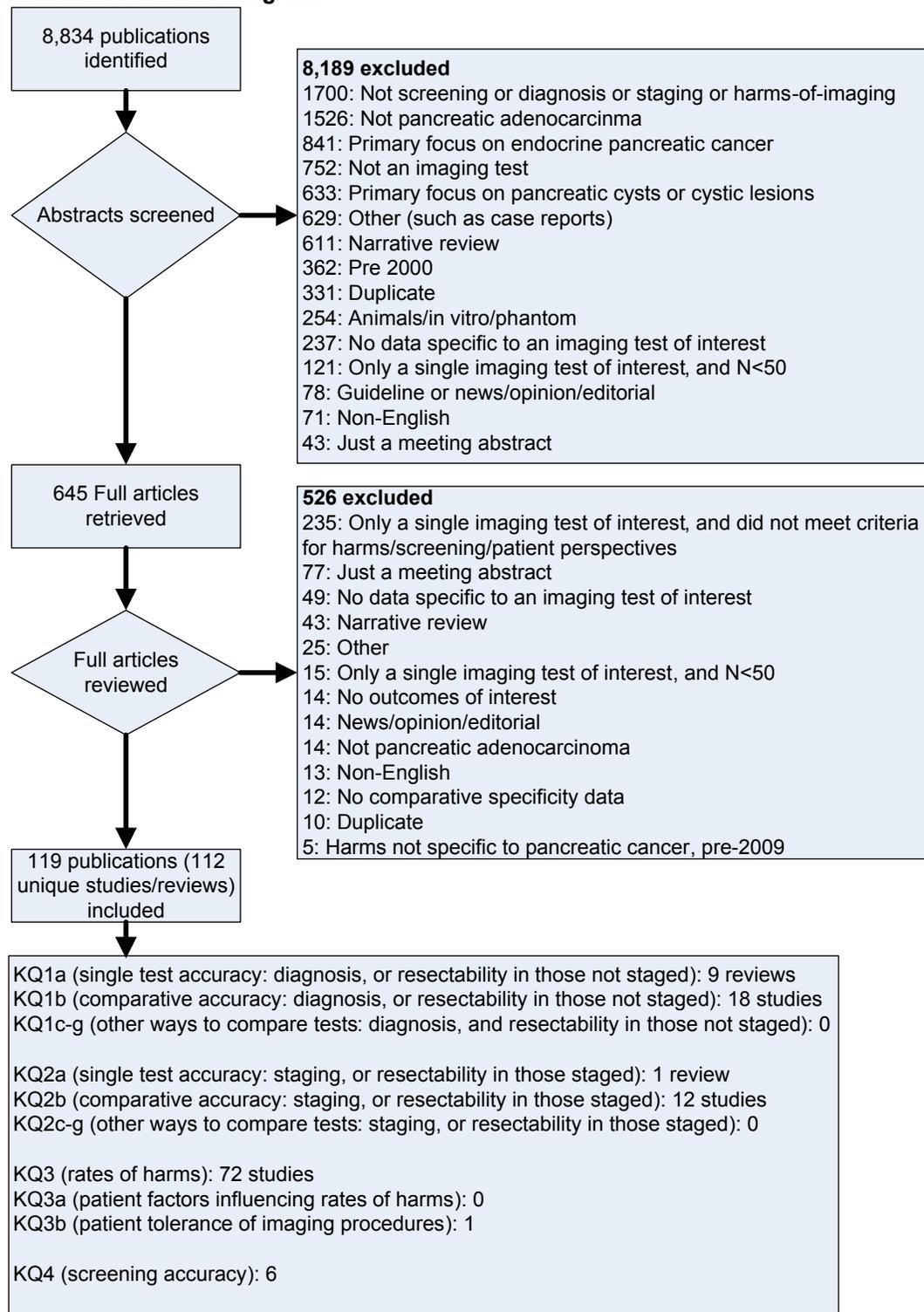
Results of Literature Searches

We summarize the study selection process in Figure 2 below. The literature searches identified 8,834 citations, and after duplicate review, we excluded 8,189 of them. The most common reason for exclusion was that the article did not involve diagnosis, staging, screening, or harms. We retrieved the other 645 articles in full, and after duplicate review, we excluded 526 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 key questions. See Appendix B for a list of the publications excluded at the full article level. We included the remaining 119 publications, which described 112 unique studies/reviews (seven publications reported overlapping patients). Of the 112, 10 were systematic reviews and 102 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.

Evidence tables in Appendix C provide all information that we abstracted from systematic reviews (KQ1a, and KQ2a), comparative accuracy studies (the rest of KQ1 and KQ2), harms studies (KQ3), and screening studies (KQ4). For the latter three sets of studies, we provide separate tables for general study information (e.g., country, enrollment dates, funding source), patient information (e.g., enrollment criteria, age, sex, diagnoses), imaging test information (e.g., test parameters, radioactive tracer[s] used, needles used for FNA), and pertinent data. Our quantitative analyses of comparative accuracy are summarized in Appendix D, along with the risk-of-bias assessments.

Figure 2. Literature flow diagram



Note: the numbers in the box above add to more than 112 because some studies/reviews addressed multiple Key Questions.

Test Performance of Imaging Modalities for Diagnosis

Key Question 1: What is the comparative effectiveness of imaging techniques (e.g., multidetector computed tomography [MDCT] angiography with or without 3D reconstruction, other MDCT, endoscopic ultrasound with fine-needle aspiration [EUS-FNA], positron emission tomography–computed tomography [PET/CT], magnetic resonance imaging [MRI]) for diagnosis of pancreatic adenocarcinoma in adults with suspicious symptoms?

Key Question 1a. What is the accuracy of each imaging technique for diagnosis and assessment of resectability?

Key Points

- 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 percent confidence interval [CI], 86 percent to 94 percent) and a specificity estimate of 85 percent (95 percent CI, 76 percent to 91 percent).
- 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.
- 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.
- 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.
- For MDCT, in assessing the resectability of tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 81 percent (95 percent CI, 76 percent to 85 percent) and a specificity estimate of 82 percent (95 percent CI, 77 percent to 97 percent).
- For MRI, in assessing the resectability tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 82 percent (95 percent CI, 69 percent to 91 percent) and a specificity estimate of 78 percent (95 percent CI, 63 percent to 87 percent).

Detailed Synthesis

Nine systematic reviews met the inclusion criteria for this question, of which three 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 described in Evidence Table C-1, and their quality assessment is in Evidence Table C-2, both of Appendix C. The three recent high-quality reviews included only evidence on EUS-FNA and not on any of the other diagnostic modalities.

Diagnosis

For EUS-FNA in diagnosing pancreatic cancer, the three recent high-quality reviews²⁶⁻²⁸ reported summary sensitivity results ranging from 85 percent to 93 percent and summary specificity results ranging from 94 percent to 100 percent (Evidence Table C-3 of 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,²⁶ 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,²⁹ which was deemed not of high quality. It also is outdated, having been published in 2005.

MRI was addressed in three reviews,²⁹⁻³¹ none of which were high quality. Two of the reviews^{30,31} 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 one review,³⁰ histopathologic analysis or clinical and imaging followup in the other³¹). 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 most recent data in the third review²⁹ is now 10 years old, and thus it does not reflect the current state of the art in MRI.

PET/CT was addressed in two reviews,^{30,32} neither of which were high quality. The review by Wu et al. (2012)³⁰ reported an erroneous confidence interval on sensitivity (82 percent to 81 percent), 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 low quality of all the reviews on CT, MRI, and PET/CT limit the confidence one can have in the quantitative estimates of accuracy.

Resectability

The only review that included resectability as an outcome was outdated, of low quality, and analyzed only CT and magnetic resonance imaging (MRI) studies (Table 4). It found a statistically insignificant difference in sensitivity favoring MRI and a statistically insignificant difference in specificity favoring CT (Table C-3 of Appendix C). Because of the low quality of the review and the large confidence intervals on the authors’ summary estimates, we conclude that the evidence is inadequate to prove any difference in effectiveness between CT and MRI.

Table 3. Key Question 1a: summary results of systematic reviews on diagnosis

Modality	MDCT	EUS-FNA	MRI	PET/CT
Number of reviews	1	3	3 (2 mostly duplicative of each other)	2
Quality of reviews	Low	High	Low	Low
Most recent review	2005	2013	2012	2012
Range of results	Sensitivity: 91 percent Specificity: 85 percent	Sensitivity: 85 percent to 93 percent Specificity: 94 percent to 100 percent	Sensitivity: 84 percent to 86 percent Specificity: 82 percent to 91 percent	Sensitivity: 87 percent to 90 percent Specificity: 80 percent to 83 percent

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

Table 4. Key Question 1a: summary results of systematic reviews on resectability

Modality	MDCT	EUS-FNA	MRI	PET/CT
Number of reviews	1	0	1	0
Quality of reviews	Low	—	Low	—
Most recent review	2005	—	2005	—
Range of results	Sensitivity: 81 percent Specificity: 82 percent	—	Sensitivity: 82 percent Specificity: 78 percent	—

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

Comparative Test Performance of Imaging Modalities for Diagnosis

Key Question 1b. What is the comparative accuracy of the different imaging techniques for diagnosis and assessment of resectability?

Key Points

- MDCT and EUS-FNA are approximately equally accurate in the assessment of resectability of pancreatic adenocarcinoma in unstaged symptomatic adults (Strength of evidence: low)
- MDCT and MRI are approximately equally accurate 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 Key Question 1b or Key Question 2b on comparative accuracy for staging (or met criteria for both Key Question 1b and Key Question 2b). 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 study⁵⁰ comparing EUS-FNA to MDCT was authored by individuals receiving grant money from the American Society of 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,⁴³ comparing MDCT angiography with versus 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.

The remainder of this section is divided into subsections based on the comparisons made by included studies (listed in Table 5 below).

Table 5. Key Question 1b: 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=combined position emission tomography and computed tomography

MDCT Angiography With 3D Reconstruction Versus Without 3D Reconstruction

One study⁴³ addressed this comparison, 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 authored by the developers of the 3D reconstruction software under consideration. We performed a statistical comparison of the sensitivity of MDCT without 3D reconstruction (89 percent; 95 percent CI, 68 percent to 97 percent) to the sensitivity of MDCT with 3D reconstruction (100 percent; 95 percent CI, 83 percent to 100 percent), 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 percent; 95 percent CI, 91 percent to 100 percent) was more accurate than MDCT without 3D reconstruction (79 percent; 95 percent CI, 64 percent to 89 percent); 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. 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 studies compared these technologies with respect to diagnostic accuracy. Two were judged as moderate risk-of-bias, and one was judged as low risk of bias. We performed a meta-analysis of the three studies and found summary sensitivities for MDCT and EUS-FNA of

87 percent (95 percent CI, 82 percent to 91 percent) and 89 percent (95 percent CI, 85 percent to 93 percent), respectively, and we found summary specificities of 67 percent (95 percent CI, 53 percent to 78 percent) and 81 percent (95 percent CI, 68 percent to 90 percent). This evidence suggests a slight advantage of EUS-FNA, however statistical tests reveal no statistically significant differences, and we judged the evidence as too imprecise to permit a conclusion of approximate equivalence (particularly notable was the uncertainty around specificities). Thus, we drew no conclusion.

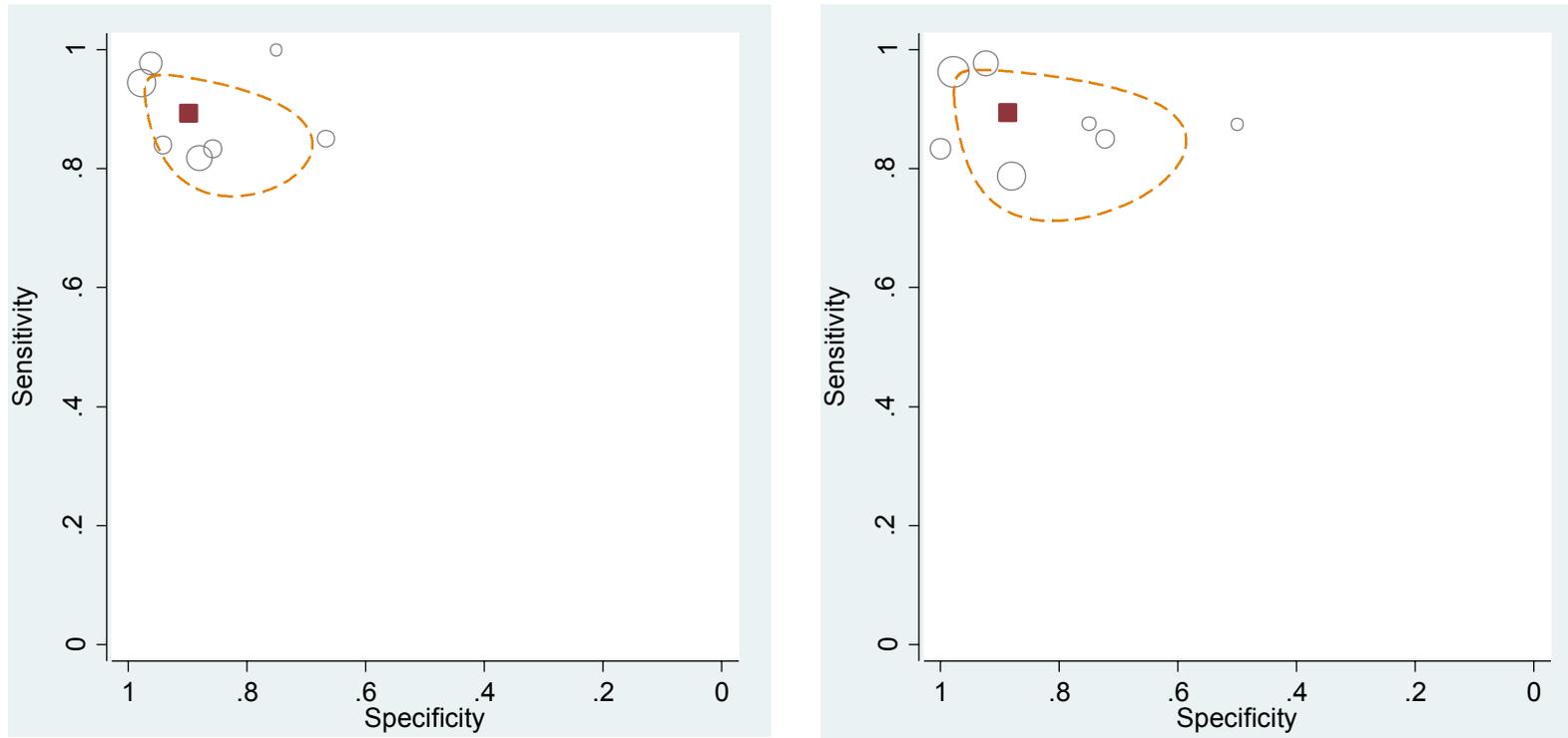
One study compared MDCT and EUS-FNA for the assessment of resectability in those with disease not staged. The study was judged to have low risk of bias, and it found similar accuracy for the two technologies (truly unresectable patients were correctly deemed unresectable at rates of 64 percent and 68 percent for MDCT and EUS-FNA, respectively; and patients with truly resectable disease were correctly deemed resectable at rates of 92 percent and 88 percent for MDCT and EUS-FNA, respectively). We judged the study to be sufficiently precise to permit a conclusion of approximate equivalence. However, consistency was unknown, which limits the confidence one can have in the conclusion. Based on the study's prevalence 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, and those whose disease is deemed resectable by either test have about a 70 percent chance of their disease actually being resectable.

MDCT Versus MRI

Seven studies compared MDCT and MRI with respect to diagnostic accuracy. Four were low risk of bias, and three were moderate risk of bias. Our meta-analysis found summary sensitivities of 89 percent for both technologies (95 percent CIs of 82 percent to 94 percent for MDCT and 81 percent to 91 percent for MRI), and summary specificities of 90 percent for MDCT (95 percent CI, 80 percent to 95 percent) and 89 percent for MRI (95 percent CI, 74 percent to 95 percent). These data we judged sufficiently precise to indicate approximate equivalence. Plots in receiver operating characteristic (ROC) space appear in Figure 3 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 to $\tau=0.6$ 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 six 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.

Figure 3. ROC plot of diagnostic accuracy, MDCT versus MRI



The left side of the plot shows the MDCT data in receiver operating characteristic (ROC) space; the right side shows the 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 percent 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 considered the possibility of publication bias in a quantitative manner. We 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 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 ($R^2=0.11$).

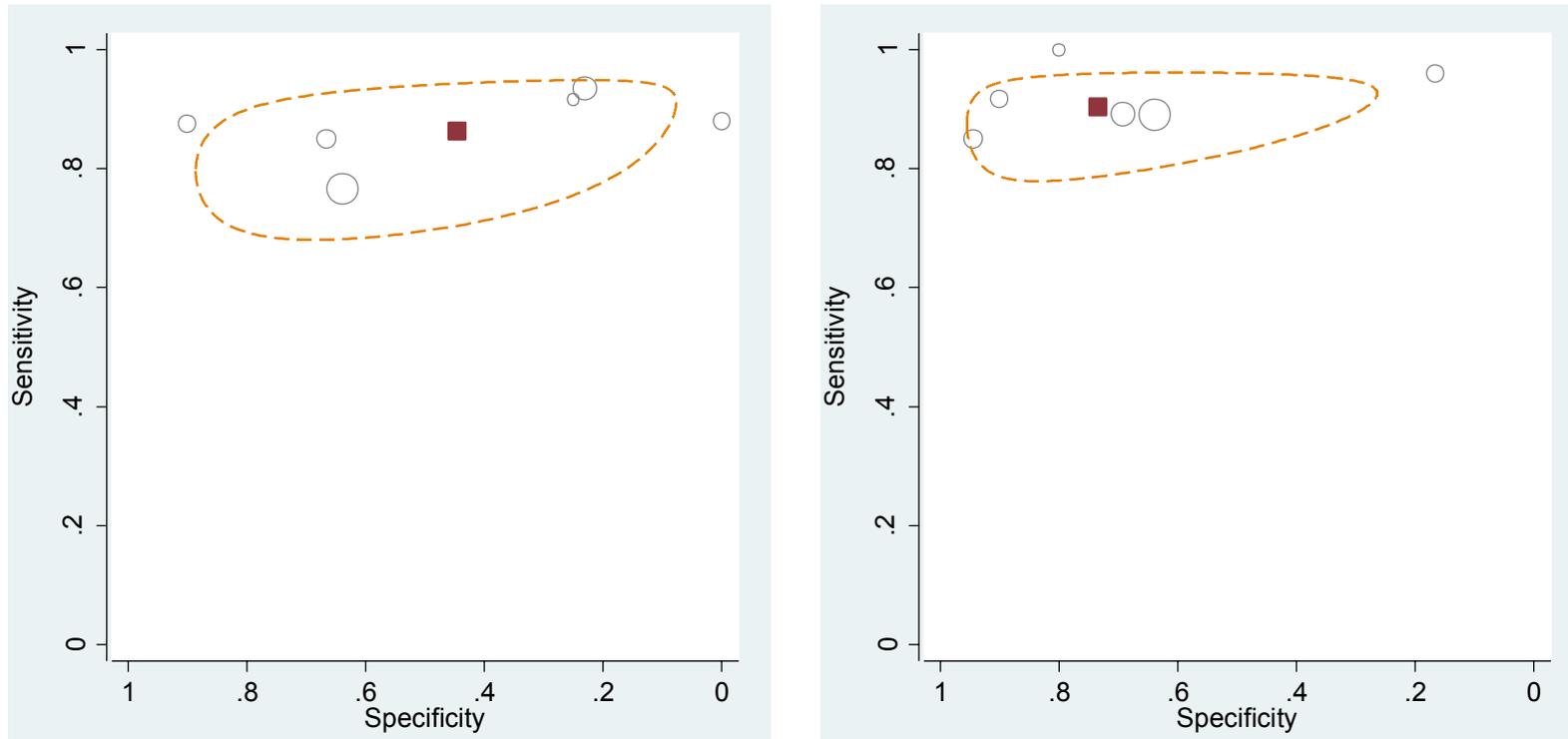
Two studies compared MDCT and MRI for the assessment of resectability in patients with disease not staged; both were judged low risk of bias. Our meta-analysis of the two studies yielded summary sensitivities for MDCT and MRI of 68 percent (95 percent CI, 47 percent to 85 percent) and 52 percent (95 percent CI, 31 percent to 72 percent), respectively, and we found summary specificities of 89 percent (95 percent CI, 77 percent to 96 percent) and 91 percent (95 percent CI, 80 percent to 97 percent). These suggest no clear direction of effect (statistical tests not significant), and we judged the data too imprecise to indicate equivalence, thus we drew no conclusion.

MDCT Versus PET/CT

Six studies compared MDCT and PET/CT with respect to diagnostic accuracy. Two were low risk of bias, and four were moderate risk of bias. Our meta-analysis found summary sensitivities of 85 percent (95 percent CI, 80 percent to 90 percent) for MDCT and 91 percent (95 percent CI, 85 percent to 94 percent) for PET/CT, and summary specificities of 55 percent for MDCT (95 percent CI, 44 percent to 66 percent) and 72 percent for PET/CT (95 percent CI, 61 percent to 81 percent). 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 4 below. These plots show large uncertainty around specificity estimates (horizontal ovals), and this uncertainty explains why the apparent specificity difference (55 percent for MDCT vs. 72 percent 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 4. ROC plot of diagnostic accuracy, MDCT versus PET/CT



The left side of the plot shows the MDCT data in receiver operating characteristic (ROC) space; the right side shows the 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 percent confidence interval range around the summary estimate.

For the above meta-analysis of six studies, we considered the possibility of publication bias in a quantitative manner. We 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 study⁵¹ 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 percent; 95 percent CI, 62 percent to 91 percent; vs. PET/CT, 89 percent; 95 percent CI, 72 percent to 96 percent) or specificity (EUS-FNA, 84 percent; 95 percent CI, 62 percent to 94 percent, vs. PET/CT, 74 percent; 95 percent CI, 51 percent to 88 percent). Furthermore, we judged the evidence too imprecise to conclude approximate equivalence. Thus, no conclusion is warranted.

MRI Versus PET/CT

One study⁵² 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 percent; with 95 percent CI, 64 percent to 95 percent; vs. PET/CT, 85 percent; 95 percent CI, 64 percent to 95 percent) or specificity (MRI, 72 percent; 95 percent CI, 49 percent to 87 percent; vs. PET/CT, 94 percent; 95 percent CI, 74 percent to 99 percent). Furthermore, we judged the evidence too imprecise to conclude approximate equivalence. Thus, no conclusion is warranted.

For other subquestions under Key Question 1(c through g), no included studies reported pertinent data.

Conclusions for Key Question 1

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 percent CI, 86 percent to 94 percent) and a specificity estimate of 85 percent (95 percent CI, 76 percent to 91 percent).
- 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.
- 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.
- 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.
- For MDCT, in assessing the resectability tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 81 percent (95 percent CI, 76 percent to 85 percent) and a specificity estimate of 82 percent (95 percent CI, 77 percent to 97 percent).
- For MRI, in assessing the resectability of tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 82 percent (95 percent CI, 69 percent

to 91 percent) and a specificity estimate of 78 percent (95 percent CI, 63 percent to 87 percent).

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 fifth 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 Key Question 1b:

- MDCT and EUS-FNA are approximately equally accurate in the assessment of resectability of pancreatic adenocarcinoma in symptomatic adults with unstaged disease (Strength of evidence: low)
- MDCT and MRI are approximately equally accurate in the diagnosis of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate)

Table 6. Summary of evidence on Key Question 1b

Comparison	Clinical Decision	# Studies	Risk of Bias	Directness	Consistency	Precision	Publication Bias	Strength of Evidence	Conclusion
MDCT angiography without 3D reconstruction vs. with 3D reconstruction	Resectability in those with unstaged disease	1 ⁴³	Low	Direct	Unknown	Precise	Yes	Insufficient	NA
MDCT vs. EUS-FNA	Diagnosis	3 ^{50,53,54}	2 Moderate, 1 Low	Direct	Inconsistent	Imprecise	No	Insufficient	NA
MDCT vs. EUS-FNA	Resectability in those not staged	1 ⁵⁰	Low	Direct	Unknown	Precise	No	Low	Approximate equivalence
MDCT vs. MRI	Diagnosis	7 ⁵⁵⁻⁶¹	4 Low, 3 Moderate	Direct	Consistent	Precise	No	Moderate	Approximate equivalence
MDCT vs. MRI	Resectability in those not staged	2 ^{58,62}	Low	Direct	Consistent	Imprecise	No	Insufficient	NA
MDCT vs. PET/CT	Diagnosis	6 ^{59,63-67}	4 Moderate, 2 Low	Direct	Consistent	Imprecise	No	Insufficient	NA
EUS-FNA vs. PET/CT	Diagnosis	1 ⁵¹	Moderate	Direct	Unknown	Imprecise	No	Insufficient	NA
MRI vs. PET/CT	Diagnosis	1 ⁵⁹	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

Test Performance of Imaging Modalities for Staging

Key Question 2: What is the comparative effectiveness of imaging techniques (e.g., MDCT angiography with or without 3D reconstruction, other MDCT, EUS-FNA, PET/CT, MRI) for staging of pancreatic adenocarcinoma among adults with a diagnosis of pancreatic adenocarcinoma?

Key Question 2a. 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

- One low-quality systematic review published in 2009 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 and specificity of CT to be 85 percent (95 percent CI, 78 percent to 91 percent) and 82 percent (95 percent CI, 74 percent to 88 percent), respectively.

Detailed Synthesis

Only one systematic review²⁶ addressed this question (Table C-4 of Appendix C). It is a low-quality review (risk-of-bias assessment in Table D-2 of Appendix D) of CT studies that included studies that used single-slice CT scanners. Rather than using the TNM system of staging, it examined only the question of whether the primary tumor had invaded surrounding vasculature. The authors reported summary results for both the total of studies included and for the subset of studies published between 2004 and 2008, most of which used multi-slice CT. Sensitivity was considerably higher for the later studies than for the rest (Table C-4 of Appendix C), with no corresponding loss of specificity.

Comparative Test Performance of Imaging Modalities for Staging

Key Question 1b. 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 are approximately equally accurate 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 metastases of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate)

- 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 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 7 below).

Table 7. Key Question 2b: 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	2	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 study 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 percent by MDCT, vs. 67 percent by EUS-FNA), the percentage whose disease was overstaged (14 percent by MDCT, 18 percent by EUS-FNA), and the percentage whose disease was understaged (44 percent by MDCT, and 14 percent by EUS-FNA). We computed the relative risk of accurate staging as 0.61 (95 percent CI, 0.41 to 0.90), which statistically favors EUS-FNA. However, consistency was unknown, which limits the confidence one can have in the conclusion.

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

MDCT Versus MRI

One study compared MDCT and MRI with respect to T staging. MDCT yielded an accurate T stage on 73 percent, whereas MRI yielded an accurate staged in 62 percent. The resulting relative risk is 1.17 (95 percent CI, 0.90 to 1.52), and this result is neither statistically significant nor indicative of equivalence, so we did not draw conclusions.

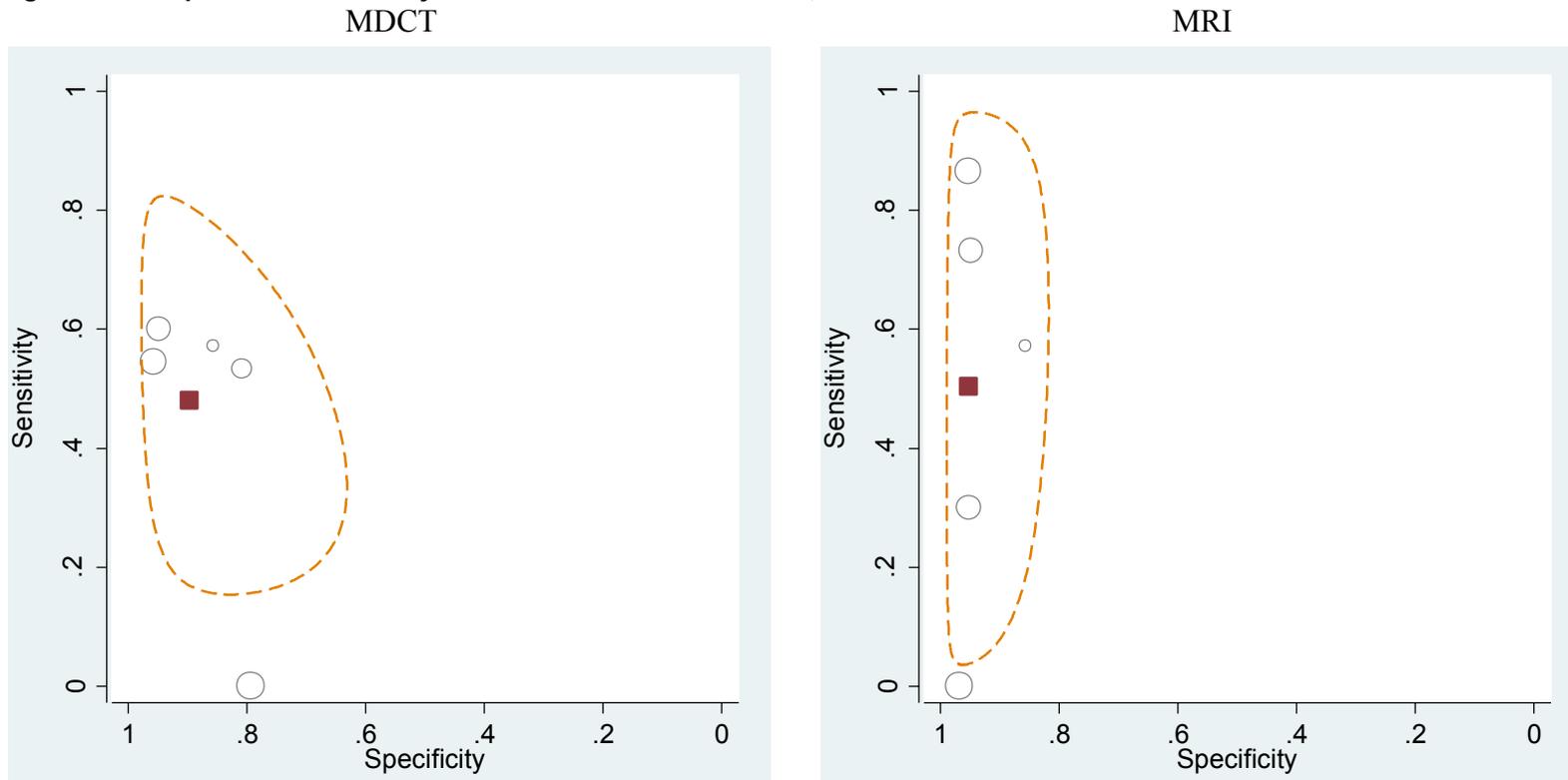
One study compared these technologies with respect to N staging. Results statistically favored neither technology for either sensitivity (MDCT, 38 percent; 95 percent CI, 21 percent to 57 percent; vs. MRI, 15 percent; 95 percent CI, 5 percent to 36 percent) or specificity (MDCT,

79 percent; 95 percent CI, 63 percent to 90 percent; vs. MRI, 93 percent; 95 percent CI, 78 percent to 98 percent). Furthermore, we judged the evidence too imprecise to conclude approximate equivalence. Thus, no conclusion is warranted.

Five studies compared these technologies with respect to the assessment of metastases. Our meta-analysis yielded sensitivity estimates of 48 percent (95 percent CI, 31 percent to 66 percent) and 50 percent (95 percent CI, 19 percent to 81 percent) for MDCT and MRI, respectively. For specificity, the meta-analytic estimates were 90 percent (95 percent CI, 81 percent to 95 percent) and 95 percent (95 percent CI 91 percent to 98 percent) 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 5 below. 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 percent, 73 percent, 57 percent, 30 percent, and 0 percent in the five studies).

Figure 5. ROC plot of the accuracy of assessment of metastases, MDCT versus MRI



The left side of the plot shows the MDCT data in receiver operating characteristic (ROC) space; the right side shows the 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 (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 analysis 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 considered the possibility of publication bias in a quantitative manner. We 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), 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 study compared MDCT and MRI for the assessment of precise stage. MDCT was accurate in 46 percent and MRI was accurate in 36 percent, resulting in a relative risk of 1.28 (95 percent CI, 0.81 to 2.01). We judged these data too imprecise to indicate equivalence.

Two studies compared these technologies for the assessment of vessel involvement (both low risk of bias). The meta-analysis found similar accuracy (sensitivity 68 percent for MDCT with 95 percent CI, 55 percent to 79 percent; and 62 percent for MRI with 95 percent CI, 48 percent to 74 percent; specificity 97 percent for MDCT with 95 percent CI, 94 percent to 98 percent; and 96 percent for MRI with 95 percent CI 93 percent to 98 percent). We judged this as sufficient evidence for concluding equivalent accuracy. Given the median prevalence of 13 percent, we estimate that a positive test result (on either MDCT or MRI) indicates a 73 percent chance of vessel involvement, whereas a negative test result (on either test) indicates only a 5 percent chance.

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

MDCT Versus PET/CT

One study compared MDCT and PET/CT with respect to N staging. Study results suggested approximate equivalence:

- 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 compared these technologies with respect to the assessment of metastases. Our meta-analysis yielded summary sensitivities of 57 percent (95 percent CI, 36 percent to 75

percent) and 67 percent (95 percent CI, 47 percent to 83 percent) for MDCT and PET/CT, respectively, and the summary specificities were 91 percent (95 percent CI 81 percent to 97 percent) and 100 percent (95 percent CI 95 percent to 100 percent) for MDCT and PET/CT, respectively. The difference in specificity was statistically significant in favor of PET/CT. The sensitivities were not statistically significant different; however, they were in the same direction. One of the two studies was moderate risk of bias, and the other 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.

To help interpret the data, we note that the two studies had a median 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.

EUS-FNA Versus MRI

One study compared EUS-FNA and MRI for the assessment of precise stage. EUS-FNA provided an accurate stage in 71 percent of patients (34/48), whereas MRI did so in 75 percent (36/48). The relative risk was 0.94 (95 percent CI, 0.74 to 1.21), which is sufficiently precise to indicate equivalence. However, it was only a single, moderate risk-of-bias study; thus, we drew no conclusions.

MRI Versus PET/CT

One study 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 percent; 95 percent CI, 25 percent to 84 percent; vs. PET/CT, 86 percent; 95 percent CI, 48 percent to 97 percent) or specificity (MDCT, 86 percent; 95 percent CI, 48 percent to 97 percent; vs. PET/CT, 94 percent; 95 percent CI, 64 percent to 100 percent). Furthermore, we judged the evidence too imprecise to conclude approximate equivalence. Thus, no conclusion is warranted.

For other subquestions under Key Question 2 (c through g), no included studies reported pertinent data.

Conclusions for Key Question 2

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 and specificity of CT to be 85 percent (95 percent CI, 78 percent to 91 percent) and 82 percent (95 percent CI, 74 percent to 88 percent), respectively.

For comparative test accuracy of staging and resectability in patients with staged disease, our assessments of the evidence are summarized in Table 8 below. Of the 12 sets of evidence listed in the table, we deemed seven 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 Key Question 2b:

- 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 are approximately equally accurate 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 metastases of pancreatic adenocarcinoma in symptomatic adults (Strength of evidence: moderate)

Table 8. Summary of evidence on Key Question 2b

Comparison	Clinical Decision	# Studies	Risk of Bias	Directness	Consistency	Precision	Publication Bias	Strength of Evidence	Conclusion
MDCT vs. EUS-FNA	T staging	1 ⁵⁰	Low	Direct	Unknown	Precise	No	Low	Evidence favors EUS-FNA
MDCT vs. EUS-FNA	Vessel involvement	1 ⁶⁸	Moderate	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI	T staging	1 ⁶⁹	Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI	N staging	1 ⁶⁹	Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI	Metastases	5 ^{57,59,69-71}	4 Low, 1 Moderate	Direct	Inconsistent	Imprecise	No	Insufficient	NA
MDCT vs. MRI	Precise stage	1 ⁶⁹	Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. MRI	Vessel involvement	2 ^{58,62}	Low	Direct	Consistent	Precise	No	Moderate	Approximate equivalence
MDCT vs. MRI	Resectability in those staged	1 ⁶⁹	Low	Direct	Unknown	Imprecise	No	Insufficient	NA
MDCT vs. PET/CT	N staging	1 ⁶⁷	Moderate	Direct	Unknown	Precise	No	Insufficient	NA
MDCT vs. PET/CT	Metastases	2 ^{59,72}	1 Moderate, 1 Low	Direct	Consistent	Precise	No	Moderate	Evidence favors PET/CT
EUS-FNA vs. MRI	Precise stage	1 ⁷³	Moderate	Direct	Unknown	Precise	No	Insufficient	NA
MRI vs. PET/CT	Metastases	1 ⁵⁹	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

Key Question 3: What are the rates of harms of imaging techniques (e.g., MDCT angiography with or without 3D reconstruction, other MDCT, EUS-FNA, PET/CT, MRI) when used to diagnose and/or stage pancreatic adenocarcinoma?

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 percent to 2.4 percent), postprocedural pain (0.1 percent to 2.0 percent), and bleeding/puncture/perforation (0 percent to 4.3 percent).

Detailed Synthesis

We included 72 studies for this KQ. Forty-four 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. Pancreas-specific studies were published from 1991 to 2011, and studies evaluated as few as 50 patients⁷⁴ or as many as 1,034 patients.⁷⁵ One study by Eloubeidi et al. (2004)⁷⁶ 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.⁷⁶ 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 1993.⁷⁷ Studies evaluated as few as 1 patient or as many as 106,000 patients.⁷⁸ 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.^{54,79} Sakamoto et al. (2008)⁷⁹ enrolled 119 patients suspected of having a pancreatic solid tumor because of abdominal screening findings on EUS 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)⁵⁴ 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 patients. 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 post procedural 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 percent to 61.5 percent [all moderate]) were evaluated in more than 180,497 patients in 12 studies.^{78,80-90} Most studies evaluated CT, however three studies evaluated CT and CT angiography^{82,83,88} and two studies evaluated CT coronary angiography.^{87,89} Eight studies included at-risk patients.^{80,81,83-87,89}

Non-ionic contrast agents, introduced in the 1970s, have a lower osmolarity than blood and are therefore less likely to cause adverse reactions.⁹⁰ Non-ionic contrast agents evaluated included iopromide,^{78,80,83,90} iomeprol,^{80,81,90} iohexol,^{80,81,88} iopamidol,^{81,82,87,89,90} iodixanol,^{80,89} and ioversol.^{81,85,90}

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.⁸² 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 delayed adverse reactions from iohexol (N=258) compared with controls (N=281).⁸⁸ Delayed adverse reactions are typically defined as occurring 1 hour or more after administration of a contrast medium.⁸⁸ 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)⁸³ 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 percent).

Cadwallar et al. (2011)⁸⁶ reported results from 198 scans of at-risk patients to determine the risk of fatal cancer induction. Forty-one (20.7 percent) 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 2,000.⁹¹

Two studies reported only mild-to-moderate harms;^{80,89} two studies included at-risk patients.^{80,89} Six studies however reported serious/severe adverse events;^{78,81,84,85,87,90} five (42 percent) studies enrolled at-risk patients.^{81,84,85,87,90} Two studies reported 15 deaths within 45 days⁸⁴ after CT. Mitchell et al. (2012)⁸⁴ 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 percent vs. 8 percent) and congestive heart failure (12 percent vs. 5 percent). Seventy patients (11 percent) developed CIN; slightly more CTPA than non-CTPA patients (14 percent vs. 10 percent). All-cause 45-day mortality rate was slightly higher in CTPA patients (3 percent vs. 2 percent) with 15 deaths during this time. Three patients with 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)⁸¹ reported 23 (0.06 percent) 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 percent) or hypertensive (28.6 percent). Vogl et al. (2012)⁸⁵ reported anaphylactoid adverse reactions requiring hospitalization in 4 (0.03 percent) 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)⁹⁰ 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)⁷⁸ and one case of atrial fibrillation (patient on peritoneal dialysis),⁸⁷ 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, and perforation/puncture/bleeding. Thirteen studies reported that there were no harms or complications resulting from EUS-FNA procedures.^{74,92-103}

Twenty-one studies reported pancreatitis as an adverse event.^{75,76,92,101,104-121} 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 2.4 percent. Thirteen studies indicated patients experienced mild or acute pancreatitis,^{76,104-107,109,112-115,117,118,120} two studies reported moderate pancreatitis,^{75,110} and one study reported severe pancreatitis.⁷⁵ Seven did not specify whether pancreatitis was mild/acute, moderate, or severe.^{101,107,108,111,116,119,121} Table 9 below provides further details.

Table 9. Rates of pancreatitis after EUS-FNA

Study	Pancreatitis Details	Rate of Harm
Ikezawa et al. 2012 ¹⁰⁴	Mild pancreatitis treated conservatively	1.8% (1/56)
Siddiqui et al. 2012 ¹⁰⁵	Mild acute pancreatitis (resolved within 1 day)	0.3% (2/677)
Beane et al. 2011 ¹⁰⁶	Acute pancreatitis requiring hospital admission and conservative treatment	1.1% (2/179)
Fisher et al. 2011 ¹¹⁹	Pancreatitis	2.4% (4/170)
Iglesias-Garcia et al. 2011 ¹¹⁸	Mild acute pancreatitis, requiring hospitalization for 4–5 days	1.1% (2/182)
Kopelman et al. 2011 ¹⁰⁷	Any morbidity other than mild pancreatitis	0% (0/102)
	Mild pancreatitis resolved spontaneously	1% (1/102)
Carrara et al. 2010 ⁷⁵	Moderate acute pancreatitis	0.1% (1/1034)
	Severe acute pancreatitis	0.1% (1/1034)
Chang et al. 2009 ¹²¹	"Clinical" pancreatitis (did not define "clinical")	0% (0/139)

Study	Pancreatitis Details	Rate of Harm
Fisher et al. 2009 ¹⁰⁸	Pancreatitis	0% (0/93)
Yusuf et al. 2009 ¹²⁰	Mild pancreatitis	1.3% (11/842)
Eloubeidi et al. 2007 ^{109,122-126}	Major complication: acute pancreatitis	0.9% (5/547)
Mahnke et al. 2006 ¹¹⁰	Moderate pancreatitis	0.3% (1/310)
Bournet et al. 2006 ¹¹¹	Pancreatitis	0.4% (1/224)
Mortensen et al. 2005 ¹¹²	Acute pancreatitis	0.1% (1/670)
Ryozawa et al. 2005 ¹⁰¹	Pancreatitis	0% (0/52)
Eloubeidi et al. 2004 ⁷⁶	Acute pancreatitis	0.3% (14/4909)
Gress et al. 2002 ¹¹³	Acute pancreatitis	2% (2/100)
Harewood and Wiersema 2002 ¹¹⁴	Mild pancreatitis requiring 2-day hospital stay	0.5% (1/185)
Gress et al. 2001 ¹¹⁶	Pancreatitis	1% (1/102)
O'Toole et al. 2001 ¹¹⁵	Acute pancreatitis	1.2% (3/248)
Voss et al. 2000 ¹¹⁷	Acute pancreatitis	0% (0/99)

Nine studies reported pain as an adverse event.^{79,105,108,109,117,127-130} The number of patients at risk of pain ranged from 28 to 677, and the mean age range was 62–66.4 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.^{79,105,109,117,128,130} Table 10 below provides further details.

Table 10. Rates of pain after EUS-FNA

Study	Pain Details	Rate of Harm
Siddiqui et al. 2012 ¹⁰⁵	Abdominal pain	0.1% (1/677)
Kliment et al. 2010 ¹²⁷	Minor pain treated with a single dose of analgesics	1% (2/207)
Fisher et al. 2009 ¹⁰⁸	Pain requiring hospital re-admission	1.1% (1/93)
Zamboni et al. 2009 ¹²⁹	Pain after the procedure, not clinically significant	1.1% (6/545)
Al-Haddad et al. 2008 ¹³⁰	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 ⁷⁹	Abdominal pain, transient	2.0% (2/98)
Shah et al. 2008 ¹²⁸	Abdominal pain	1.6% (2/123)
Eloubeidi et al. 2007 ^{109,122-126}	Major complication: severe pain	0.5% (3/547)
	Minor complication: abdominal pain	0.9% (5/547)
Voss et al. 2000 ¹¹⁷	Abdominal pain and pyrexia, resolved spontaneously	1% (1/99)

Eighteen studies reported perforation/puncture/bleeding as an adverse event.^{75,79,101,105,108-112,116-119,127,128,131-134} 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/bleeding ranged from 52 to 1,034, and the mean age range was 47–68.2 years. The range of rates reported for perforation/puncture/bleeding was 0 percent to 4.3 percent. Table 11 below provides further details.

Table 11. Rates of bleeding/perforation/puncture after EUS-FNA

Study	Perforation/Puncture/Bleeding Details	Rate of Harm
Hayashi et al. 2013 ¹³¹	Punctures resulting in peripancreatic abscess and requiring antibiotics	0.7% (1/138)
Ootaki et al. 2012 ¹³²	Self-limited bleeding during or after EUS-FNA (in conscious sedation group)	0.5% (2/371)

Study	Perforation/Puncture/Bleeding Details	Rate of Harm
Siddiqui et al. 2012 ¹⁰⁵	Significant intra-procedural bleeding after FNA	0% (0/677)
	Bowel perforations	0% (0/677)
Fisher et al. 2011 ¹¹⁹	Bleeding (self limited)	0% (0/170)
	Perforation	0.6% (1/170)
	Bile leak	0.6% (1/170)
Iglesias-Garcia et al. 2011 ¹¹⁸	Bleeding at site of gastric puncture	0.5% (1/182)
Itoi et al. 2011 ¹³³	Procedure-related bleeding, treated by conservative therapy without blood transfusion	0.6% (2/356)
Carrara et al. 2010 ⁷⁵	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 ¹²⁷	Minor bleeding without treatment necessary	1.5% (3/207)
Fisher et al. 2009 ¹⁰⁸	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 ⁷⁹	Bleeding from FNA site	0% (0/98)
Shah et al. 2008 ¹²⁸	Periduodenal bleeding	0.8% (1/123)
Eloubeidi et al. 2007 ^{109,122-126}	Minor complication: exaggerated bleeding	0.4% (2/547)
Rocca et al. 2007 ¹³⁴	Minor intracystic hemorrhage	0.3% (1/293)
Bournet et al. 2006 ¹¹¹	Upper gastrointestinal bleeding	0.4% (1/224)
	Perforation, duodenal	0.4% (1/224)
Mahnke et al. 2006 ¹¹⁰	Mild bleeding	0.3% (1/310)
Mortensen et al. 2005 ¹¹²	Massive gastrointestinal bleeding	0.1% (1/670)
Ryozawa et al. 2005 ¹⁰¹	Hemorrhage	0% (0/52)
	Perforation	0% (0/52)
Gress et al. 2001 ¹¹⁶	Substantial gastric mucosal bleeding with clot formation	2.0% (2/102)
Voss et al. 2000 ¹¹⁷	Bleeding	4% (4/99)

Three studies^{79,92,101} specifically reported that tumor seeding after EUS-FNA had not occurred; these studies had enrolled a total of 244 patients. Additionally, other complications, such as infection, brief hypoxia, and reversal of medication, were reported. Four studies reported infection, with rates ranging from 0 percent to 6.7 percent.^{101,106,110,111} Two studies reported brief hypoxia,^{106,109} with rates ranging from 0.3 percent to 0.6 percent, and two studies reported reversal of medication usage,^{109,110} with rates ranging from 0.2 percent to 0.6 percent.

Recent Harms Studies Not Specific to Pancreatic Cancer

Katanuma et al. (2013)¹³⁵ 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 percent CI, 3.55 to 96.17; p<0.001) and pancreatic neuroendocrine tumors (OR, 36.50; 95 percent 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 percent to 14.4 percent [mostly minor]) were reported in more than 21,088 patients in five studies.¹³⁶⁻¹⁴⁰ Two studies enrolled at-risk patients and focused on sedation-related complications.^{136,137} One study enrolled 799 patients (more than 60 percent classified as ASA Class III)¹³⁶ (see Appendix C for further details). In multivariate analysis, male sex (OR, 1.75; 95 percent CI, 1.08 to 2.85; p=.02), ASA class 3 or more (OR, 1.90; 95 percent CI, 1.11 to 3.25; p=.02), and body mass index (OR, 1.05; 95 percent CI, 1.01 to 1.09; p=.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 percent ASA Class IV).¹³⁷ Of the 151 patients enrolled, 34 patients underwent EUS. No significant differences were reported in overall cardiopulmonary complication rates.

Forty-two (0.4 percent) serious adverse events were reported by Niv et al. (2011)¹³⁹ in a 7-year retrospective review of physician reporting. Harms from EUS and endoscopic retrograde cholangiopancreatography (ERCP) included perforation (69 percent), bleeding (4.8 percent), cardiovascular and respiratory (4.8 percent), teeth trauma (2.4 percent) and other (19 percent). “Critical outcomes” for the 42 patients involved included 15 mortality cases (35.7 percent) and 18 (42.9 percent) 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.¹³⁸ Eloubeidi et al. (2009)¹⁴⁰ reported cervical esophageal perforations in three (0.06 percent) 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)¹³⁸ reported 9 (0.2 percent) EUS-related harms including desaturation, supraventricular tachycardia, and gallbladder and duodenal perforations. Jenssen et al. (2012) indicated that gastrointestinal perforations from EUS typically occurred as follows:¹⁴¹

- At areas of angulation (e.g., rectosigmoidal junction)
- In the presence of unexpected anatomical alterations (e.g., duodenal diverticula)
- In luminal obstruction (e.g., gastrointestinal cancer)

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 percent to 64.6 percent) were evaluated in more than 156,962 patients in 11 studies.^{77,78,142-150} Adverse events from contrast-enhanced MRIs were the focus of 10 (91 percent) studies.^{77,78,142-149} Contrast agents such as gadobenate dimeglumine (Gd-BOPTA),¹⁴² gadobutrol (Gd-BT-DO3A),^{77,142,145,149} gadoterate meglumine (Gd-DOTA),^{144,147} gadopentetate dimeglumine (Gd-DTPA)^{77,78} gadodiamide (Gd-DTPA-BMA),⁷⁷ gadoversetamide (Gd-DTPA-BMEA),⁷⁷ gadoxetic acid disodium salt (Gd-EOB-DTPA),¹⁴⁶ gadoteridol (Gd-HP-DO3A),⁷⁷ manganese chloride tetrahydrate (CMC-001),¹⁴³ and oral manganese (McCl₂)¹⁴⁸ were administered in nine studies. (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.¹⁵¹ Although relatively safe in most patients, contrast agents may be quite harmful to others.

The American College of Radiology (ACR) Manual on Contrast Media (2013) 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.¹⁵² 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.¹⁵³

The ACR Manual on Contrast Media¹⁵² 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.¹⁵⁴ The 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.¹⁵⁵ 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.¹⁵⁶

Six MRI-related studies enrolled at-risk patients;^{77,144,146,147,149,150} five studies evaluated GBCAs in patients at-risk for kidney or liver disease.^{77,144,146,147,149} The largest study (N=84,621) surveyed 19,354 (22.9 percent) 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 percent) or automated (25.5 percent) injections of Gd-DOTA.¹⁴⁴ In the study, 421 adverse events (65 different) occurred in 285 (0.34 percent) patients. Eight serious adverse events (less than 0.01 percent) were reported; life-threatening events in 3 patients. Ishiguchi and Takahashi¹⁴⁷ 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 lesions¹⁴⁶ after undergoing MRI with a single injection of Gd-EOB-DTPA. Voth et al. (2011)⁷⁷ 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 percent) although slightly more serious adverse events occurring in the Gd-BT-DO3A group (0.4 percent vs. 0.2 percent). Lastly, Hammerstingl et al. (2009)¹⁴⁹ 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,¹⁴² mild gastrointestinal harms,¹⁴⁸ mild burns from an MR coil,⁷⁸ and two severe adverse drug reactions (ADRs).^{143,145} One integrated retrospective analysis of six clinical studies¹⁴⁵ (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 MRI¹⁵⁰ enrolled 365 patients at-risk for developing breast cancer and reported significant MRI discomfort was mainly due to noise of the machine (64.6 percent). 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.⁷⁸ A retrospective review of 3,359 PET/CT scans (106,800 scans overall)⁷⁸ 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.

Key Question 3a. How are patient factors related to the harms of different imaging techniques?

No included studies addressed this subquestion.

Key Question 3b. 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.¹⁵⁷ 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 either a first-degree relative with pancreatic cancer or anyone with a gene mutation prone to pancreatic cancer. The screening examinations involved both endoscopic ultrasound and magnetic resonance imaging, 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 Key Question 3

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

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/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

Key Question 4: What is the screening accuracy of imaging techniques (e.g., MDCT angiography with or without 3D reconstruction, other MDCT, 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)?

Key Points

- No accuracy estimates are possible for any single imaging modality because the six included screening studies provided only accuracy data for a joint set of imaging tests.
- The large majority of HRIs who undergo screening for pancreatic adenocarcinoma either have completely normal imaging studies (52 percent to 63 percent) or have some abnormal imaging that was not sufficiently concerning to warrant biopsy or surgery (18 percent to 45 percent).
- Only 2 percent to 18 percent of HRIs screened received either a biopsy or surgery based on imaging findings (any imaging modality— MDCT, EUS with or without FNA, MRI), amounting to a total of 46 HRIs (7 percent) from the 6 studies.
- Of the total of 46 patients with a pathological specimen from either biopsy or surgery from all 6 screening studies, 17 total (1.1 percent to 9.0 percent of HRIs screened) had true-positive findings (i.e., pathology-confirmed precursor lesions or pancreatic adenocarcinoma); 19 total (0 percent to 9.8 percent of HRIs screened) had a 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); 7 total (0 percent to 9.2 percent of HRIs screened) had a minor false-positive finding (i.e., patient had a FNA biopsy based on imaging and pathology was normal, no surgery performed); 3 (0 percent to 1.5 percent of HRIs screened) had false-negative findings (i.e., patient's cancer was missed on image screening but found later with pathology confirmation).

Detailed Synthesis

Six primary studies met inclusion criteria for this question, of which five were recent (published 2009 or later). The group of studies was heterogeneous in the population studied, imaging tests examined, the design of study, and reporting of results, which limits generation of conclusions. Studies defined 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 study¹⁵⁸ screened only individuals with a known *p16* gene mutation, which is associated with various cancers and found most prominently in pancreatic cancer. One study had a control arm of non-HRIs,¹⁵⁹ however, we examined only the data on HRIs. Two studies^{160,161} 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.

One study¹⁵⁸ 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 also ERCP. 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. Individual study observations suggest that CT alone as an imaging modality for screening HRI may be insufficient.^{159,160} In Canto et al.(2012),¹⁶⁰ the authors noted fewer pancreatic lesions were detected by MDCT than by MRI and EUS with or without FNA. Individual study observations also suggest that EUS with or without FNA alone may “overcall suspicious lesions,”¹⁶² but in combination with additional imaging such as MRI, it may be useful to prevent unnecessary surgery.

All six studies were prospective, and none were randomized controlled trials. One study¹⁵⁹ had a control arm of 149 non-HRIs. Two studies^{159,160} 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 unaware of clinical or radiologic findings.¹⁵⁹ In two studies,^{159,163} only one endoscopist performed all EUS procedures, and in two studies,^{159,162} 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 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 that 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,¹⁶⁰ standard of care for surveillance and treatment was determined by each individual site. This is also further complicated by both new understanding in the field and some differing opinions of what warrants surgery. The currently held belief is that branch duct-type IPMNs and low-grade PanIN (pancreatic intraepithelial neoplasia; grade 1 and 2) do not universally warrant surgical resection.

Data tables in Appendix D summarize the overall 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 with or without 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 percent) from all six studies (total N=653) 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 incidence of 0.082 percent. However an appropriate 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 percent of all enrolled HRIs from 6 studies, with individual studies ranging from 2 percent to 18 percent 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)¹⁶⁰ acknowledged a more conservative approach and had a lower rate of true positives along with Al-Sukhni.¹⁶² However Al-Sukhni also had two cases of false negatives where biopsy-confirmed cancer lesions and precursor lesions were found on subsequent imaging screenings (4th and 5th rounds) that were not seen on initial imaging. While 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 Canto et al. (2012)¹⁶⁰ study did not, however, report any false negatives, but the authors also focused on a one-time initial screening and had an average followup period of 28 months, perhaps not allowing for additional cases of undetected pancreatic cancers to be detected or captured. Higher rates of true positives in studies Verna,¹⁶¹ Vassen,¹⁵⁸ and Canto¹⁵⁹ (4.9 percent, 9.0 percent, 5.1 percent, respectively), also had higher rates of major false positives (5.1 percent to 9.8 percent) in which 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. 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.

Conclusions for Key Question 4

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. Therefore, studies did not uniformly nor comprehensively report results for each imaging modality performed, which prevents conclusions about accuracy for any particular imaging tests 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^{159,161,162} extrapancreatic neoplasms were detected among HRIs (located in ovaries, kidneys, lung). In some studies, MDCT missed lesions that were detected through EUS.¹⁵⁹

- Some studies report that MRI/MRCP has similar abilities to detect precursor lesions.¹⁶³ However 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 appear to include detection of pancreatic masses smaller than 1 cm. FNA also allows for tissue sampling to aid in diagnosis. Disadvantages to EUS include that it is less readily available, more operator dependent, and more invasive than other imaging modalities. Authors of one study believe that EUS “overcalled” or overdiagnosed suspicious lesions, leading to unnecessary surgical resection.¹⁵⁹ Studies reviewed have suggested the use of EUS as an adjunct to another screening modality such as CT or MR.^{159,162} 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. Basic questions of whether such screening or surveillance programs in HRIs is warranted and improves prognosis are still unclear.

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, in particular those with strong genetic predispositions. In a few studies,^{158,159,162} cases were apparent in which the defined interval between screens was deemed appropriate, yet may not have been. However, rapid progression and cancer development occurred in some cases, 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 to determine the most effective approach to screening for pancreatic cancer.

There is also an evolution in the understanding of precursor lesions such as IPMN and PanIN lesions. One consensus-based guideline published in 2012 suggested that main duct intraductal papillary mucinous neoplasia (MD-IPMN) should be resected, whereas BD-IPMN without high-risk features (i.e, high-grade dysplasia, increasing size) should be monitored.

Current imaging technologies are insufficient to differentiate between the low-grade and high-grade dysplasia in IPMNs and PanINs. As mentioned earlier, currently, those with higher-grade dysplasia often have precursor lesions that may develop into cancer, while those with low-grade dysplasia are considered to have benign lesions. This creates a difficult situation when an IPMN or PanIN is suspected on imaging, and in the studies examined in this evidence report, resulted in several pancreatic resections that perhaps were unnecessary. Surgical resection is currently the main treatment for precursor lesions; however, timing of surgery intervention versus continued surveillance needs further study. Given the potential morbidity and mortality associated with pancreatic surgery, clarification of the uncertain significance of certain precursor lesions, as well as the timing of surgery is needed.

Discussion

Key Findings and Strength of Evidence

For single-test accuracy, we summarized results from relevant systematic reviews to estimate the accuracy of each individual imaging modality. For 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 percent confidence interval [CI], 86 percent to 94 percent) and a specificity estimate of 85 percent (95 percent CI, 76 percent to 91 percent).
- For diagnosis using endoscopic ultrasound with fine-needle aspiration (EUS-FNA), three high-quality, recent systematic reviews yielded sensitivity estimates ranging from 83 percent to 92 percent and specificity estimates ranging from 95 percent to 100 percent.
- For diagnosis using magnetic resonance imaging (MRI), three systematic reviews yielded sensitivity estimates of 84 percent to 85 percent and specificity estimates of 82 percent to 91 percent.
- For diagnosis using positron emission tomography–computed tomography (PET/CT), two systematic reviews yielded sensitivity estimates of 87 percent and 90 percent and specificity estimates of 83 percent and 90 percent.
- For MDCT, in assessing the resectability of tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 81 percent (95 percent CI, 76 percent to 85 percent) and a specificity estimate of 82 percent (95 percent CI, 77 percent to 97 percent).
- For MRI, in assessing the resectability of tumors in patients with unstaged disease, one systematic review yielded a sensitivity estimate of 82 percent (95 percent CI, 69 percent to 91 percent) and a specificity estimate of 78 percent (95 percent CI, 63 percent to 87 percent).

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

- One low-quality systematic review published in 2009 addressed this question, and assessed the accuracy of computed tomography (CT) in assessing vascular involvement.
- When the review considered only studies published since 2004, the review estimated the sensitivity and specificity of CT to be 85 percent (95 percent CI, 78 percent to 91 percent) and 82 percent (95 percent CI, 74 percent to 88 percent), respectively.

For comparative accuracy, our conclusions appear in Table 12. 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 also an important finding, because MDCT is the standard, many tumors are unstaged, and the key clinical decision is whether 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).

Turning to staging, we found T staging to be better with EUS-FNA than MDCT, but this is a less important finding since, as stated earlier, the key clinical issue is resectability. One key input to resectability is the involvement of blood vessels, and we found that MDCT and MRI are similarly accurate for vessel assessment. Another input to the resectability decision is metastasis, and we found that PET/CT has a slight advantage over MDCT in this area (about a 10 percentage-point advantage for both sensitivity and specificity). We note that both technologies had poor accuracy in detecting metastases (sensitivities of 57 percent for MDCT and 67 percent for PET/CT) but were quite good at ruling out metastases (specificities of 91 percent for MDCT and 100 percent for PET/CT).

Table 12. Summary of conclusions

Conclusion	# Studies	Risk of Bias	Directness	Consistency	Precision	Publication Bias	Strength of Evidence
MDCT and MRI are approximately equally accurate in the diagnosis of pancreatic adenocarcinoma in symptomatic adults	7	4 Low, 3 Moderate	Direct	Consistent	Precise	No	Moderate
MDCT and EUS-FNA are approximately equally accurate in the assessment of resectability of pancreatic adenocarcinoma in symptomatic adults with unstaged disease	1	Low	Direct	Unknown	Precise	No	Low
EUS-FNA is more accurate than MDCT in the assessment of the T stage of pancreatic adenocarcinoma in symptomatic adults	1	Low	Direct	Unknown	Precise	No	Low
MDCT and MRI are approximately equally accurate in the assessment of the vessel involvement of pancreatic adenocarcinoma in symptomatic adults	2	Low	Direct	Consistent	Precise	No	Moderate
PET/CT is more accurate than MDCT in the assessment of metastases of pancreatic adenocarcinoma in symptomatic adults	2	1 Moderate, 1 Low	Direct	Consistent	Precise	No	Moderate

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

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, 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/bleeding. Regarding patient tolerance, one study of screening found that about 10 percent of patients state that EUS-FNA and MRI are very uncomfortable.

For screening, most people at high risk of developing pancreatic adenocarcinoma have negative results on pertinent imaging tests. Available studies do not correlate the results of a given imaging test to subsequent diagnoses; therefore, one cannot determine the screening accuracy of any given imaging test.

Findings in Relationship to What is Already Known

We identified four reviews whose purpose was to compare different imaging modalities for the diagnosis and/or staging of pancreatic adenocarcinoma. One⁴⁹ 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 four 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 Key Question 3.

Wu et al. (2012)³⁰ 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 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)³² 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 percent, vs. 88 percent for PET alone and 81 percent for EUS), whereas EUS was the most specific (93 percent, vs. 80 percent for PET/CT and 83 percent for PET alone). 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)⁴⁹ 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, 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 approximate equivalence. 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)²⁹ 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 percent to 83 percent) 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.

Regarding procedural harms, one systematic review summarized data on EUS-FNA.¹⁶⁴ 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 Key Question 3. It was not. For pancreatitis, findings were in the opposite direction (0.39 percent for prospective studies, 0.46 percent for retrospective studies). For pain, findings were in the same direction, but the difference was smaller (1 percent in prospective studies, 0.7 percent 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 still 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% 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) most commonly utilized for diagnosing, staging, and determining the resectability of pancreatic cancer. In this report, the evidence was usually too imprecise to permit conclusions, but we did find sufficient evidence for some tentative evidence-based conclusions, outlined next.

For diagnosis, we found MDCT and MRI are approximately equivalent 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 MDCT vs. PET/CT, EUS-FNA vs. PET/CT, or MRI vs. PET/CT did not allow us to draw conclusions regarding comparative accuracy for diagnosis, due to 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 approximately equivalent to MDCT (detailed below).

In the staging assessment of metastases (M staging), PET/CT was more accurate than MDCT. A positive MDCT indicates an 80 percent chance of actually having metastases (i.e. PPV of 80 percent), whereas a positive PET/CT indicates a near 100 percent chance (i.e. PPV of 100 percent). A negative MDCT indicates a 23 percent chance of having metastases (i.e. NPV 23%), whereas a negative PET/CT 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 the assessment of 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 percent), whereas a negative test result (on either test) indicates only a 5 percent chance (i.e. NPV of 5 percent). For determining resectability of those not staged, MDCT and EUS-FNA were found to be approximately equivalent in accuracy. Those who are deemed unresectable by either MDCT or EUS-FNA have about an 88 percent chance of actually being unresectable (i.e. PPV of 88 percent), and those who are deemed resectable by either test have about a 70 percent chance of actually being resectable (i.e. PPV of 70 percent). 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.

MDCT angiography (CTA) with 3D reconstruction is a newer technology, for which no conclusions could be drawn in this review due to limited evidence. One study that was performed by the software developers of the technology suggested a greater ability of CTA 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 that remains is that while our key questions 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, these four imaging studies are not all equally available. Each study has its associated risks of harms as well as patient preferences and tolerances. MDCT is the most widely available, and although it is associated the least amount of operator/interpreter dependence it does have the potential of harms from radiation exposure and administration of contrast dye. MRI and PET/CT are the next most available. These examinations are associated with slightly more operator/interpreter dependence and while PET/CT does expose patients to radiation (both through CT technique as well as radioactive isotopes), MRI does not. Finally EUS-FNA is a highly specialized procedure that is currently less-widely available than the other modalities examined. This procedure is associated with the most amount of operator dependence and also associated with the most harms including post-procedure pancreatitis, pain, GI perforation and bleeding. However, EUS-FNA does enable tissue biopsy, unlike the other imaging modalities. Patient perspectives identified in the literature were from studies screening high risk populations for pancreatic cancer, where both EUS-FNA and MRI were found in 10% and 11% 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.

Currently, there are no high grade evidence based clinical practice guidelines on which imaging modalities to use in diagnosing and staging of pancreatic cancer. Existing practice follows a multi-modality paradigm that is largely institution-specific based on technology and resource availability and institution and provider preference. This approach 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 various 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 pre-operative evaluation.

Similarly, there is no guideline or uniform approach for pancreatic cancer screening among asymptomatic high risk individuals that is widely accepted. The USPSTF recommends against screening for pancreatic cancer among the general population (i.e., average risk persons) due to the low incidence of this disease. Consensus statements on approaches to a risk-based approach to screening exist 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 high risk individuals at this time. Others have suggested that imaging, genetic and tumor marker evaluation should be restricted to the context of research. Our goal was not to determine if 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 high risk individuals includes multiple imaging procedures and in some cases include genetic (i.e. *p16*, *BRCA2*) and/or tumor marker (i.e, CEA, CA19-9) testing in addition to imaging. Inconsistent utilization and reporting of imaging, genetic and tumor markers in screened individuals creates significant difficulty in comparing various imaging modalities within a study and also comparing 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 high risk individuals including preferred imaging modalities.

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,³³ 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, but because of the greater likelihood of complicating comorbidities among older patients, test results may be more accurate among younger patients. Comparative accuracy, however, may be unaffected. 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 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. Such 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)¹⁶⁵ 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 percent 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. After peer review, we will address substantive issues raised by peer reviewers that did not result in major changes to our report. First, we discuss the following key issues: (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 taken and then analyzed. 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 this decision was supported by our Technical Experts.

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 should 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 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 publication bias in the context of our searches of clinicaltrials.gov as well as our quantitative analyses of publication bias.

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 sensitivities of about 50 percent (MDCT sensitivity was 48 percent with a 95 percent CI from 31 to 66 percent, as compared to MRI with a sensitivity of 50 percent and a 95 percent CI from 19 percent to 82 percent). 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 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 records that suggest the existence of older unpublished trials whose publication may have been suppressed. We identified four relevant records:

- One (NCT00920023) was last updated in March 2013 and involved only a single imaging test (MRI); therefore, it would be included only for our Key Question 3 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, therefore may be published in the future.
- A third (NCT00816179) was still recruiting as of October 2013 and involves only EUS-FNA; such studies sometimes meet our inclusion criteria for harms, so it should be considered during updates.

- A fourth (NCT01717196) is 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.

Research Gaps

For characterizing gaps, we used the Hopkins EPC framework proposed by Robinson et al. (2011).¹⁶⁶ 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 reason A, 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 information in the context of diagnosis and staging of pancreatic adenocarcinoma; thus, the reason for this gap is A, 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 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, 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 A, insufficient or imprecise information.

The fourth important gap concerns the screening of asymptomatic high-risk people. No studies have reported test-specific screening accuracy. 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 should 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 should 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 lived longer. This would represent direct evidence on the most important outcome, survival.

Randomized trials may be far in the future, 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, symptomatology varies 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.

References

1. American Cancer Society (ACS). Cancer facts & figures 2012. Atlanta (GA): American Cancer Society (ACS); 2012. 65 p. Also available: <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf>.
2. Sharma C, Eltawil KM, Renfrew PD, et al. Advances in diagnosis, treatment and palliation of pancreatic carcinoma: 1990-2010. *World J Gastroenterol*. 2011 Feb 21;17(7):867-97. PMID: 21412497
3. Pancreatic cancer. [internet]. Bethesda (MD): National Cancer Institute (NCI); [accessed 2013 Mar 13]. [2 p]. Available: <http://www.cancer.gov/cancertopics/types/pancreatic>.
4. Dabizzi E, Assef MS, Raimondo M. Diagnostic management of pancreatic cancer. *Cancers*. 2011 Mar;3(1):494-509.
5. Pancreatic cancer treatment (PDQ). Health professional version. [internet]. Bethesda (MD): National Cancer Institute (NCI); 2012 Jul 17 [accessed 2012 Nov 8]. [27 p]. Available: <http://www.cancer.gov/cancertopics/pdq/treatment/pancreatic/HealthProfessional/page1/AllPages/Print>.
6. Benson AB III, Myerson RJ, Sasson AR. Pancreatic, neuroendocrine GI, and adrenal cancers. In: *Cancer management: a multidisciplinary approach*. 14th ed. [internet]. New York (NY): UBM Medica LLC; 2011 Oct 28 [accessed 2013 Feb 28]. Available: <http://www.cancernetwork.com/cancer-management/pancreatic/article/10165/1802606>.
7. Tamm EP, Balachandran A, Bhosale PR, et al. Imaging of pancreatic adenocarcinoma: update on staging/resectability. *Radiol Clin North Am*. 2012 May;50(3):407-28. PMID: 22560689
8. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol*. 2009 Jul;16(7):1727-33. PMID: 19396496
9. Wong JC, Lu DS. Staging of pancreatic adenocarcinoma by imaging studies. *Clin Gastroenterol Hepatol*. 2008 Dec;6(12):1301-8. PMID: 18948228
10. Chalmers I, Adams M, Dickersin K, et al. A cohort study of summary reports of controlled trials. *JAMA*. 1990 Mar 9;263(10):1401-5. PMID: 2304219
11. Neinstein LS. A review of Society for Adolescent Medicine abstracts and Journal of Adolescent Health Care articles. *J Adolesc Health Care*. 1987 Mar;8(2):198-203. PMID: 3818406
12. Dundar Y, Dodd S, Williamson P, et al. Case study of the comparison of data from conference abstracts and full-text articles in health technology assessment of rapidly evolving technologies: does it make a difference? *Int J Technol Assess Health Care*. 2006 Jul;22(3):288-94.
13. De Bellefeuille C, Morrison CA, Tannock IF. The fate of abstracts submitted to a cancer meeting: factors which influence presentation and subsequent publication. *Ann Oncol*. 1992 Mar;3(3):187-91. PMID: 1586615
14. Scherer RW, Langenberg P. Full publication of results initially presented in abstracts. In: *Cochrane Library [Cochrane methodology review]*. Issue 2. Oxford: Update Software; 2001 [accessed 2001 Apr 23]. [35 p]. Available: <http://www.cochrane.org/index.htm>.
15. Yentis SM, Campbell FA, Lerman J. Publication of abstracts presented at anaesthesia meetings. *Can J Anaesth*. 1993 Jul;40(7):632-4. PMID: 8403137

16. Marx WF, Cloft HJ, Do HM, et al. The fate of neuroradiologic abstracts presented at national meetings in 1993: rate of subsequent publication in peer-reviewed, indexed journals. *AJNR Am J Neuroradiol.* 1999 Jun-Jul;20(6):1173-7. PMID: 10445467
17. Moher D, Pham B, Klassen TP, et al. What contributions do languages other than English make on the results of meta-analyses? *J Clin Epidemiol.* 2000 Sep;53(9):964-72. PMID: 11004423
18. Juni P, Hoenstein F, Sterne J, et al. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. *Int J Epidemiol.* 2002 Feb;31(1):115-23. PMID: 11914306
19. White CM, Ip S, McPheeters M, et al. Using existing systematic reviews to replace de novo processes in conducting Comparative Effectiveness Reviews. In: *Methods guide for comparative effectiveness reviews.* Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2009 Sep. Also available: <http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60>. PMID: 21433402
20. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol.* 2003 Nov 10;3(1):25. Also available: <http://www.biomedcentral.com/content/pdf/1471-2288-3-25.pdf>. PMID: 14606960
21. Singh S, Chang S, Matchar DB, et al. Grading a body of evidence on diagnostic tests (AHRQ publication no. 12-EHC079-EF). In: *Methods guide for medical test reviews* (AHRQ publication no. 12-EHC017). Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2012 Jun 1. p. 7.1-15. Also available: <http://www.ncbi.nlm.nih.gov/books/NBK98248/#ch7.r11>.
22. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol.* 2005 Oct;58(10):982-90. PMID: 16168343
23. STATA statistics/data analysis. MP parallel edition. College Station (TX): StataCorp; 1984-2007. Single user Stata for Windows. Also available: <http://www.stata.com>.
24. Zamora J, Abraira V, Muriel A, et al. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol.* 2006;6:31. PMID: 16836745
25. Trikalinos TA, Hoaglin DC, Small KM, et al. Evaluating practices and developing tools for comparative effectiveness reviews of diagnostic test accuracy: methods for the joint meta-analysis of multiple tests. *Methods research report.* Contract no. 290-2007-10055-I. Rockville (MD): Agency for Healthcare Research and Quality; 2013 Jan. 49 p. (AHRQ publication no. 12(13)-EHC151-EF). Also available: http://effectivehealthcare.ahrq.gov/ehec/products/291/1380/Methods%20Report_Evaluating-Practices-Developing-Tools_Final_01-14-2013.pdf.
26. Madhoun MF, Wani SB, Rastogi A, et al. The diagnostic accuracy of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of solid pancreatic lesions: a meta-analysis. *Endoscopy.* 2013;45(2):86-92. PMID: 23307148
27. Chen J, Yang R, Lu Y, et al. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesion: a systematic review. *J Cancer Res Clin Oncol.* 2012 Sep;138(9):1433-41. PMID: 22752601
28. Hewitt MJ, McPhail MJW, Possamai L, et al. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: A meta-analysis. *Gastrointest Endosc.* 2012 Feb;75(2):319-31.

29. Bipat S, Phoa SS, 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):438-45. PMID: 16012297
30. Wu LM, Hu JN, Hua J, et al. Diagnostic value of diffusion-weighted magnetic resonance imaging compared with Fluorodeoxyglucose positron emission tomography/computed tomography for pancreatic malignancy: a meta-analysis using a hierarchical regression model. *J Gastroenterol Hepatol.* 2012 Jun;27(6):1027-35. PMID: 22414092
31. Wu LM, Xu JR, Hua J, et al. Value of diffusion-weighted imaging for the discrimination of pancreatic lesions: a meta-analysis. *Eur J Gastroenterol Hepatol.* 2012 Feb;24(2):134-42. PMID: 22241215
32. Tang S, Huang G, Liu J, et al. Usefulness of 18F-FDG PET, combined FDG-PET/CT and EUS in diagnosing primary pancreatic carcinoma: a meta-analysis. *Eur J Radiol.* 2011 Apr;78(1):142-50. PMID: 19854016
33. SEER stat fact sheets: pancreas. [internet]. Bethesda (MD): National Cancer Institute (NCI), National Institutes of Health (NIH); [accessed 2012 Nov 8]. [3 p]. Available: <http://seer.cancer.gov/statfacts/html/pancreas.html>.
34. Fernandez-del Castillo C. Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer. [internet]. Waltham (MA): UpToDate, Inc; 2013 Jan 14 [accessed 2013 Feb 28]. [31 p]. Available: http://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-staging-of-exocrine-pancreatic-cancer?source=search_result&search=Clinical+manifestations%2C+diagnosis%2C+and+staging+of+exocrine+pancreatic+cancer&selectedTitle=1%7E134.
35. DiMagno EP, Malagelada JR, Taylor WF, et al. A prospective comparison of current diagnostic tests for pancreatic cancer. *N Engl J Med.* 1977 Oct 6;297(14):737-42. PMID: 895803
36. Edge SB, Byrd DR, Compton CC, et al, editors. *AJCC cancer staging manual.* 7th ed. New York (NY): Springer; 2010.
37. National Comprehensive Cancer Network (NCCN). Pancreatic adenocarcinoma version 2.2012. Fort Washington (PA): National Comprehensive Cancer Network (NCCN); 2012. 94 p. Also available: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
38. Hidalgo M. Pancreatic cancer. *N Engl J Med.* 2010 Apr 29;362(17):1605-17. PMID: 20427809
39. Vincent A, Herman J, Schulick R, et al. Pancreatic cancer. *Lancet.* 2011 Aug 13;378(9791):607-20. PMID: 21620466
40. U.S. Preventive Services Task Force (USPSTF). Screening for pancreatic cancer: recommendation statement. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2004 Feb. 3 p.
41. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut.* 2012 Nov 7; Also available: <http://gut.bmj.com/content/early/2012/11/06/gutjnl-2012-303108.full.pdf+html>. PMID: 23135763
42. Quality and safety: computed tomography accreditation. [internet]. Reston (VA): American College of Radiology (ACR); [accessed 2013 May 10]. [2 p]. Available: <http://www.acr.org/Quality-Safety/Accreditation/CT>.
43. Fang CH, Zhu W, Wang H, et al. A new approach for evaluating the resectability of pancreatic and periampullary neoplasms. *Pancreatol.* 2012 Jul-Aug;12(4):364-71. PMID: 22898639
44. Quality and safety: ultrasound accreditation. [internet]. Reston (VA): American College of Radiology (ACR); [accessed 2013 May 9]. [2 p]. Available: <http://www.acr.org/Quality-Safety/Accreditation/Ultrasound>.

45. Schima W, Ba-Ssalamah A, Goetzinger P, et al. State-of-the-art magnetic resonance imaging of pancreatic cancer. *Top Magn Reson Imaging*. 2007 Dec;18(6):421-9. PMID: 18303400
46. Vachiranubhap B, Kim YH, Balci NC, et al. Magnetic resonance imaging of adenocarcinoma of the pancreas. *Top Magn Reson Imaging*. 2009 Feb;20(1):3-9. PMID: 19687720
47. Brice J. Experts put MRI accreditation program to the test. *Diagn Imaging*. 2001 Jul;23(7):44-7, 49.
48. Katanick SL. Fundamentals of ICANL accreditation. *J Nucl Med Technol*. 2005 Mar;33(1):19-23. PMID: 15731016
49. Dewitt J, Devereaux BM, Lehman GA, et al. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. *Clin Gastroenterol Hepatol*. 2006 Jun;4(6):717-25; quiz 664. PMID: 16675307
50. DeWitt J, Devereaux B, Chriswell M, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. *Ann Intern Med*. 2004 Nov 16;141(10):753-63. PMID: 15545675
51. Schick V, Franzius C, Beyna T, et al. Diagnostic impact of 18F-FDG PET/CT evaluating solid pancreatic lesions versus endosonography, endoscopic retrograde cholangio-pancreatography with intraductal ultrasonography and abdominal ultrasound. *Eur J Nucl Med Mol Imaging*. 2008 Oct;35(10):1775-85. PMID: 18481063
52. Seo Y, Kim MS, Yoo S, et al. Stereotactic body radiation therapy boost in locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2009 Dec 1;75(5):1456-61. PMID: 19783379
53. Tamm EP, Loyer EM, Faria SC, et al. Retrospective analysis of dual-phase MDCT and follow-up EUS/EUS-FNA in the diagnosis of pancreatic cancer. *Abdom Imaging*. 2007 Sep-Oct;32(5):660-7. PMID: 17712589
54. Agarwal B, Abu-Hamda E, Molke KL, et al. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. *Am J Gastroenterol*. 2004 May;99(5):844-50.
55. Rao SX, Zeng MS, Cheng WZ, et al. Small solid tumors (< or = 2 cm) of the pancreas: relative accuracy and differentiation of CT and MR imaging. *Hepatogastroenterology*. 2011 May-Jun;58(107-108):996-1001. PMID: 21830431
56. Takakura K, Sumiyama K, Munakata K, et al. Clinical usefulness of diffusion-weighted MR imaging for detection of pancreatic cancer: comparison with enhanced multidetector-row CT. *Abdom Imaging*. 2011 Aug;36(4):457-62. PMID: 21643939
57. Motosugi U, Ichikawa T, Morisaka H, et al. Detection of pancreatic carcinoma and liver metastases with Gadoteric Acid-enhanced MR imaging: comparison with contrast-enhanced multi-detector row CT. *Radiology*. 2011 Aug;260(2):446-53. PMID: 21693662
58. Koelblinger C, Ba-Ssalamah A, Goetzinger P, et al. Gadobenate Dimeglumine-enhanced 3.0-T MR imaging versus multiphasic 64-detector row CT: prospective evaluation in patients suspected of having pancreatic cancer. *Radiology*. 2011 Jun;259(3):757-66. PMID: 21436084
59. Kauhanen SP, Komar G, Seppanen MP, et al. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. *Ann Surg*. 2009 Dec;250(6):957-63. PMID: 19687736
60. Mehmet Erturk S, Ichikawa T, Sou H, et al. Pancreatic adenocarcinoma: MDCT versus MRI in the detection and assessment of locoregional extension. *J Comput Assist Tomogr*. 2006 Jul-Aug;30(4):583-90. PMID: 16845288

61. Rieber A, Tomczak R, Nussle K, et al. MRI with Mangafodipir Trisodium in the detection of pancreatic tumours: comparison with helical CT. *Br J Radiol.* 2000 Nov;73(875):1165-9. PMID: 11144793
62. Lee JK, Kim AY, Kim PN, et al. Prediction of vascular involvement and resectability by multidetector-row CT versus MR imaging with MR angiography in patients who underwent surgery for resection of pancreatic ductal adenocarcinoma. *Eur J Radiol.* 2010 Feb;73(2):310-6. PMID: 19070981
63. Casneuf V, Delrue L, Kelles A, et al. Is combined 18F-fluorodeoxyglucose-positron emission tomography/computed tomography superior to positron emission tomography or computed tomography alone for diagnosis, staging and restaging of pancreatic lesions. *Acta Gastroenterol Belg.* 2007 Oct-Dec;70(4):331-8. PMID: 18330088
64. Herrmann K, Erkan M, Dobritz M, et al. Comparison of 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography (FLT PET) and FDG PET/CT for the detection and characterization of pancreatic tumours. *Eur J Nucl Med Mol Imaging.* 2012 May;39(5):846-51. PMID: 22278320
65. Saif MW, Cornfeld D, Modarresifar H, et al. 18F-FDG positron emission tomography CT (FDG PET/CT) in the management of pancreatic cancer: initial experience in 12 patients. *J Gastrointest Liver Dis.* 2008 Jun;17(2):173-8. PMID: 18568138
66. Heinrich S, Goerres GW, Schafer M, et al. Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. *Ann Surg.* 2005 Aug;242(2):235-43.
67. Lemke A-J, Niehues SM, Hosten N, et al. Retrospective digital image fusion of multidetector CT and 18F-FDG PET: Clinical value in pancreatic lesions - A prospective study with 104 patients. *J Nucl Med.* 2004 Aug 1;45(8):1279-1286.
68. Tellez-Avila FI, Chavez-Tapia NC, Lopez-Arce G, et al. Vascular invasion in pancreatic cancer: predictive values for endoscopic ultrasound and computed tomography imaging. *Pancreas.* 2012 May;41(4):636-8. PMID: 22460727
69. Soriano A, Castells A, Ayuso C, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. *Am J Gastroenterol.* 2004 Mar;99(3):492-501. PMID: 15056091
70. Holzapfel K, Reiser-Erkan C, Fingerle AA, et al. Comparison of diffusion-weighted MR imaging and multidetector-row CT in the detection of liver metastases in patients operated for pancreatic cancer. *Abdom Imaging.* 2011 Apr;36(2):179-84. PMID: 20563868
71. Imai H, Doi R, Kanazawa H, et al. Preoperative assessment of para-aortic lymph node metastasis in patients with pancreatic cancer. *Int J Clin Oncol.* 2010 Jun;15(3):294-300.
72. Farma JM, Santillan AA, Melis M, et al. PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. *Ann Surg Oncol.* 2008 Sep;15(9):2465-71. PMID: 18551347
73. Shami VM, Mahajan A, Loch MM, et al. Comparison between endoscopic ultrasound and magnetic resonance imaging for the staging of pancreatic cancer. *Pancreas.* 2011 May;40(4):567-70. PMID: 21499211
74. Fabbri C, Polifemo AM, Luigiano C, et al. Endoscopic ultrasound-guided fine needle aspiration with 22- and 25-gauge needles in solid pancreatic masses: a prospective comparative study with randomisation of needle sequence. *Dig Liver Dis.* 2011 Aug;43(8):647-52. PMID: 21592873
75. Carrara S, Arcidiacono PG, Mezzi G, et al. Pancreatic endoscopic ultrasound-guided fine needle aspiration: complication rate and clinical course in a single centre. *Dig Liver Dis.* 2010 Jul;42(7):520-3. PMID: 19955025

76. Eloubeidi MA, Gress FG, Savides TJ, et al. Acute pancreatitis after EUS-guided FNA of solid pancreatic masses: a pooled analysis from EUS centers in the United States. *Gastrointest Endosc.* 2004 Sep;60(3):385-9. PMID: 15332028
77. Voth M, Rosenberg M, Breuer J. Safety of Gadobutrol, a new generation of contrast agents: experience from clinical trials and postmarketing surveillance. *Invest Radiol.* 2011 Nov;46(11):663-71. PMID: 21623211
78. Shah-Patel LR, Piraner M, Silberzweig JE. Adverse events in a freestanding radiology office. *J Am Coll Radiol.* 2009 Apr;6(4):263-7. PMID: 19327659
79. Sakamoto H, Kitano M, Suetomi Y, et al. Utility of contrast-enhanced endoscopic ultrasonography for diagnosis of small pancreatic carcinomas. *Ultrasound Med Biol.* 2008 Apr;34(4):525-32. PMID: 18045768
80. Kim SH, Jo EJ, Kim MY, et al. Clinical value of radiocontrast media skin tests as a prescreening and diagnostic tool in hypersensitivity reaction. *Ann Allergy Asthma Immunol.* 2013 Apr;110(4):258-62. PMID: 23535089
81. Kobayashi D, Takahashi O, Ueda T, et al. Risk factors for adverse reactions from contrast agents for computed tomograph. *BMC Med Inform Decis Mak.* 2013;13:18. PMID: 23363607
82. Davenport MS, Wang CL, Bashir MR, et al. Rate of contrast material extravasations and allergic-like reactions: effect of extrinsic warming of low-osmolality iodinated CT contrast material to 37 degrees. *Radiology.* 2012 Feb;262(2):475-84. PMID: 22106356
83. Kingston RJ, Young N, Sindhusake DP, et al. Study of patients with intravenous contrast extravasation on CT studies, with radiology staff and ward staff cannulation. *J Med Imaging Radiat Oncol.* 2012 Apr;56(2):163-7. PMID: 22498188
84. Mitchell AM, Jones AE, Tumlin JA, et al. Prospective study of the incidence of contrast-induced nephropathy among patients evaluated for pulmonary embolism by contrast-enhanced computed tomograph. *Acad Emerg Med.* 2012 Jun;19(6):618-25. PMID: 22687176
85. Vogl TJ, Wessling J, Buerke B. An observational study to evaluate the efficiency and safety of Ioversol pre-filled syringes compared with Ioversol bottles in contrast-enhanced examination. *Acta Radiol.* 2012 Oct 1;53(8):914-20. PMID: 22983259
86. Cadwallader RA, Walsh SR, Burrows B, et al. Prospective audit of cross-sectional imaging and radiation exposure in general surgical patients. *Ann R Coll Surg Engl.* 2011 Jan;93(1):6-8. PMID: 20955661
87. Hatakeyama S, Abe A, Suzuki T, et al. Clearance and safety of the radiocontrast medium Iopamidol in peritoneal dialysis patients. *Int J Nephrol.* 2011;2011:657051. PMID: 22028966
88. Loh S, Bagheri S, Katzberg RW, et al. Delayed adverse reaction to contrast-enhanced CT: a prospective single-center study comparison to control group without enhancement. *Radiology.* 2010 Jun;255(3):764-71. PMID: 20406882
89. Ozbulbul NI, Yurdakul M, Tola M. Comparison of a low-osmolar contrast medium, Iopamidol, and an iso-osmolar contrast medium, Iodixanol, in MDCT coronary angiography. *Coron Artery Dis.* 2010 Nov;21(7):414-9. PMID: 20671550
90. Jung KE, Chung J, Park BC, et al. A clinical study of cutaneous adverse reactions to nonionic contrast media in Korea. *Ann Dermatol.* 2012 Feb;24(1):22-5. PMID: 22363151
91. Fact sheet: computed tomography (CT) scans and cancer. [internet]. Bethesda (MD): National Cancer Institute (NCI); 2013 Jul 16 [accessed 2013 Jul 30]. [9 p]. Available: <http://www.cancer.gov/cancertopics/factsheet/detection/CT>.

92. Hikichi T, Irisawa A, Bhutani MS, et al. Endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic masses with rapid on-site cytological evaluation by endosonographers without attendance of cytopathologists. *J Gastroenterol.* 2009;44(4):322-8. PMID: 19274426
93. Choi ER, Jang TH, Chung YH, et al. A prospective comparison of liquid-based cytology and traditional smear cytology in pancreatic endoscopic ultrasound-guided fine needle aspiration. *Acta Cytol.* 2011 Oct;55(5):401-7.
94. Bang JY, Magee SH, Ramesh J, et al. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. *Endoscopy.* 2013 Mar 15. PMID: 23504490
95. Ranney N, Phadnis M, Trevino J, et al. Impact of biliary stents on EUS-guided FNA of pancreatic mass lesions. *Gastrointest Endosc.* 2012 Jul;76(1):76-83. PMID: 22726468
96. Attila T, Faigel DO. Endoscopic ultrasound in patients over 80 years old. *Dig Dis Sci.* 2011 Oct;56(10):3065-71. PMID: 21735087
97. Kubiliun N, Ribeiro A, Fan YS, et al. EUS-FNA with rescue fluorescence in situ hybridization for the diagnosis of pancreatic carcinoma in patients with inconclusive on-site cytopathology results. *Gastrointest Endosc.* 2011 Sep;74(3):541-7. PMID: 21752364
98. Siddiqui UD, Rossi F, Rosenthal LS, et al. EUS-guided FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. *Gastrointest Endosc.* 2009 Dec;70(6):1093-7. PMID: 19640524
99. Ramirez-Luna MA, Zepeda-Gomez S, Chavez-Tapia NC, et al. Diagnostic yield and therapeutic impact of fine-needle aspiration biopsies guided by endoscopic ultrasound in pancreatic lesions. *Rev Invest Clin.* 2008 Jan-Feb;60(1):11-4. PMID: 18589582
100. Wittmann J, Kocjan G, Sgouros SN, et al. Endoscopic ultrasound-guided tissue sampling by combined fine needle aspiration and trucut needle biopsy: a prospective study. *Cytopathology.* 2006 Feb;17(1):27-33. PMID: 16417562
101. Ryozaawa S, Kitoh H, Gondo T, et al. Usefulness of endoscopic ultrasound-guided fine-needle aspiration biopsy for the diagnosis of pancreatic cancer. *J Gastroenterol.* 2005 Sep;40(9):907-11. PMID: 16211348
102. Reddymasu SC, Gupta N, Singh S, et al. Pancreato-biliary malignancy diagnosed by endoscopic ultrasonography in absence of a mass lesion on transabdominal imaging: Prevalence and predictors. *Dig Dis Sci.* 2011 Jun;56(6):1912-16.
103. Fritscher-Ravens A, Sriram PVJ, Krause C, et al. Detection of pancreatic metastases by EUS-guided fine-needle aspiration. *Gastrointest Endosc.* 2001;53(1):65-70.
104. Ikezawa K, Uehara H, Sakai A, et al. Risk of peritoneal carcinomatosis by endoscopic ultrasound-guided fine needle aspiration for pancreatic cancer. *J Gastroenterol.* 2012 Oct 13. PMID: 23065024
105. Siddiqui AA, Fein M, Kowalski TE, et al. Comparison of the influence of plastic and fully covered metal biliary stents on the accuracy of EUS-FNA for the diagnosis of pancreatic cancer. *Dig Dis Sci.* 2012 Sep;57(9):2438-45. PMID: 22526586
106. Beane JD, House MG, Cote GA, et al. Outcomes after preoperative endoscopic ultrasonography and biopsy in patients undergoing distal pancreatectomy. *Surgery.* 2011 Oct;150(4):844-53. PMID: 22000199
107. Kopelman Y, Marmor S, Ashkenazi I, et al. Value of EUS-FNA cytological preparations compared with cell block sections in the diagnosis of pancreatic solid tumours. *Cytopathology.* 2011 Jun;22(3):174-8. PMID: 20482717

108. Fisher L, Segarajasingam DS, Stewart C, et al. Endoscopic ultrasound guided fine needle aspiration of solid pancreatic lesions: Performance and outcomes. *J Gastroenterol Hepatol.* 2009 Jan;24(1):90-6. PMID: 19196396
109. Eloubeidi MA, Varadarajulu S, Desai S, et al. A prospective evaluation of an algorithm incorporating routine preoperative endoscopic ultrasound-guided fine needle aspiration in suspected pancreatic cancer. *J Gastrointest Surg.* 2007 Jul;11(7):813-9. PMID: 17440790
110. Mahnke D, Chen YK, Antillon MR, et al. A prospective study of complications of endoscopic retrograde cholangiopancreatography and endoscopic ultrasound in an ambulatory endoscopy center. *Clin Gastroenterol Hepatol.* 2006 Jul;4(7):924-30. PMID: 16797251
111. Bournet B, Miguères I, Delacroix M, et al. Early morbidity of endoscopic ultrasound: 13 years' experience at a referral center. *Endoscopy.* 2006 Apr;38(4):349-54. PMID: 16680633
112. Mortensen MB, Frstrup C, Holm FS, et al. Prospective evaluation of patient tolerability, satisfaction with patient information, and complications in endoscopic ultrasonography. *Endoscopy.* 2005 Feb;37(2):146-53. PMID: 15692930
113. Gress F, Michael H, Gelrud D, et al. EUS-guided fine-needle aspiration of the pancreas: evaluation of pancreatitis as a complication. *Gastrointest Endosc.* 2002 Dec;56(6):864-7. PMID: 12447299
114. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. *Am J Gastroenterol.* 2002 Jun;97(6):1386-91. PMID: 12094855
115. O'Toole D, Palazzo L, Arotcarena R, et al. Assessment of complications of EUS-guided fine-needle aspiration. *Gastrointest Endosc.* 2001 Apr;53(4):470-4. PMID: 11275888
116. Gress F, Gottlieb K, Sherman S, et al. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. *Ann Intern Med.* 2001 Mar 20;134(6):459-64. PMID: 11255521
117. Voss M, Hammel P, Molas G, et al. Value of endoscopic ultrasound guided fine needle aspiration biopsy in the diagnosis of solid pancreatic masses. *Gut.* 2000 Feb;46(2):244-9. PMID: 10644320
118. Iglesias-Garcia J, Dominguez-Munoz JE, Abdulkader I, et al. Influence of on-site cytopathology evaluation on the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of solid pancreatic masses. *Am J Gastroenterol.* 2011 Sep;106(9):1705-10.
119. Fisher JM, Gordon SR, Gardner TB. The impact of prior biliary stenting on the accuracy and complication rate of endoscopic ultrasound fine-needle aspiration for diagnosing pancreatic adenocarcinoma. *Pancreas.* 2011 Jan;40(1):21-24.
120. Yusuf TE, Ho S, Pavey DA, et al. Retrospective analysis of the utility of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in pancreatic masses, using a 22-gauge or 25-gauge needle system: a multicenter experience. *Endoscopy.* 2009 May;41(5):445-8.
121. Chang YH, Sang SL, Tae JS, et al. Endoscopic ultrasound guided fine needle aspiration biopsy in diagnosis of pancreatic and peripancreatic lesions: a single center experience in Korea. *Gut Liver.* 2009 Jun;3(2):116-21.
122. Eloubeidi MA, Tamhane A. Prospective assessment of diagnostic utility and complications of endoscopic ultrasound-guided fine needle aspiration. Results from a newly developed academic endoscopic ultrasound program. *Dig Dis.* 2008;26(4):356-63. PMID: 19188728
123. Eloubeidi MA, Tamhane A, Varadarajulu S, et al. Frequency of major complications after EUS-guided FNA of solid pancreatic masses: a prospective evaluation. *Gastrointest Endosc.* 2006 Apr;63(4):622-9. PMID: 16564863

124. Eloubeidi MA, Tamhane A. EUS-guided FNA of solid pancreatic masses: a learning curve with 300 consecutive procedures. *Gastrointest Endosc.* 2005 May;61(6):700-8. PMID: 15855975
125. Eloubeidi MA, Chen VK, Eltoun IA, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy of patients with suspected pancreatic cancer: diagnostic accuracy and acute and 30-day complications. *Am J Gastroenterol.* 2003 Dec;98(12):2663-8. PMID: 14687813
126. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. *Gastrointest Endosc.* 2005 Nov;62(5):728-36.
127. Kliment M, Urban O, Cegan M, et al. Endoscopic ultrasound-guided fine needle aspiration of pancreatic masses: the utility and impact on management of patients. *Scand J Gastroenterol.* 2010 Nov;45(11):1372-9. PMID: 20626304
128. Shah SM, Ribeiro A, Levi J, et al. EUS-guided fine needle aspiration with and without trucut biopsy of pancreatic masses. *JOP.* 2008;9(4):422-30. PMID: 18648133
129. Zamboni GA, D'Onofrio M, Idili A, et al. Ultrasound-guided percutaneous fine-needle aspiration of 545 focal pancreatic lesion. *AJR Am J Roentgenol.* 2009 Dec;193(6):1691-5.
130. Al-Haddad M, Wallace MB, Woodward TA, et al. The safety of fine-needle aspiration guided by endoscopic ultrasound: a prospective study. *Endoscopy.* 2008 Mar;40(3):204-8.
131. Hayashi T, Ishiwatari H, Yoshida M, et al. Rapid on-site evaluation by endosonographer during endoscopic ultrasound-guided fine needle aspiration for pancreatic solid masses. *J Gastroenterol Hepatol.* 2013 Jan 10. PMID: 23301574
132. Ootaki C, Stevens T, Vargo J, et al. Does general anesthesia increase the diagnostic yield of endoscopic ultrasound-guided fine needle aspiration of pancreatic masses. *Anesthesiology.* 2012 Nov;117(5):1044-50. PMID: 23042221
133. Itoi T, Tsuchiya T, Itokawa F, et al. Histological diagnosis by EUS-guided fine-needle aspiration biopsy in pancreatic solid masses without on-site cytopathologist: a single-center experience. *Dig Endosc.* 2011 May;23 Suppl 1:34-8. PMID: 21535198
134. Rocca R, De Angelis C, Daperno M, et al. Endoscopic ultrasound-fine needle aspiration (EUS-FNA) for pancreatic lesions: effectiveness in clinical practice. *Dig Liver Dis.* 2007 Aug;39(8):768-74. PMID: 17606420
135. Katanuma A, Maguchi H, Yane K, et al. Factors predictive of adverse events associated with endoscopic ultrasound-guided fine needle aspiration of pancreatic solid lesions. *Dig Dis Sci.* 2013 Feb 20. PMID: 23423501
136. Cote GA, Hovis RM, Ansstas MA, et al. Incidence of sedation-related complications with Propofol use during advanced endoscopic procedures. *Clin Gastroenterol Hepatol.* 2010 Feb;8(2):137-42. PMID: 19607937
137. Schilling D, Rosenbaum A, Schweizer S, et al. Sedation with Propofol for interventional endoscopy by trained nurses in high-risk octogenarians: a prospective, randomized, controlled study. *Endoscopy.* 2009 Apr;41(4):295-8. PMID: 19340730
138. Kalaitzakis E, Varytimiadis K, Meenan J. Predicting what can go wrong at endoscopic ultrasound: a large series experience. *Frontline Gastroenterol.* 2011 Apr;2(2):110-6.
139. Niv Y, Gershtansky Y, Kenett RS, et al. Complications in endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS): analysis of 7-year physician-reported adverse events. *Drug Healthc Patient Saf.* 2011;3:21-5. PMID: 21753900

140. Eloubeidi MA, Tamhane A, Lopes TL, et al. Cervical esophageal perforations at the time of endoscopic ultrasound: a prospective evaluation of frequency, outcomes, and patient management. *Am J Gastroenterol*. 2009 Jan;104(1):53-6. PMID: 19098849
141. Jenssen C, Alvarez-Sanchez MV, Napoleon B, et al. Diagnostic endoscopic ultrasonography: assessment of safety and prevention of complication. *World J Gastroenterol*. 2012 Sep 14;18(34):4659-76. PMID: 23002335
142. Semelka RC, Hernandez Mde A, Stallings CG, et al. Objective evaluation of acute adverse events and image quality of Gadolinium-based contrast agents (Gadobutrol and Gadobenate Dimeglumine) by blinded evaluation. Pilot study. *Magn Reson Imaging*. 2013 Jan;31(1):96-101. PMID: 22898688
143. Albiin N, Kartalis N, Bergquist A, et al. Manganese chloride tetrahydrate (CMC-001) enhanced liver MRI: evaluation of efficacy and safety in healthy volunteer. *MAGMA*. 2012 Oct;25(5):361-8. PMID: 22399275
144. Maurer M, Heine O, Wolf M, et al. Tolerability and diagnostic value of Gadoteric Acid in the general population and in patients with risk factors: results in more than 84,000 patients *Eur J Radiol*. 2012 May;81(5):885-90. PMID: 21555197
145. Forsting M, Palkowitsch P. Prevalence of acute adverse reactions to Gadobutrol--a highly concentrated macrocyclic Gadolinium chelate: review of 14,299 patients from observational trials. *Eur J Radiol*. 2010 Jun;74(3):e186-92. PMID: 19574008
146. Ichikawa T, Saito K, Yoshioka N, et al. Detection and characterization of focal liver lesions: a Japanese phase III, multicenter comparison between Gadoxetic Acid Disodium-enhanced magnetic resonance imaging and contrast-enhanced computed tomography predominantly in patients with hepatocellular carcinoma and chronic liver disease. *Invest Radiol*. 2010 Mar;45(3):133-41. PMID: 20098330
147. Ishiguchi T, Takahashi S. Safety of Gadoterate Meglumine (Gd-DOTA) as a contrast agent for magnetic resonance imaging: results of a post-marketing surveillance study in Japan. *Drugs R D*. 2010;10(3):133-45. PMID: 20945944
148. Leander P, Golman K, Mansson S, et al. Orally administered Manganese with and without Ascorbic Acid as a liver-specific contrast agent and bowel marker for magnetic resonance imaging: phase I clinical trial assessing efficacy and safety. *Invest Radiol*. 2010 Sep;45(9):559-64. PMID: 20644487
149. Hammersting R, Adam G, Ayuso J-RA, et al. Comparison of 1.0 M Gadobutrol and 0.5 m Gadopentetate Dimeglumine-enhanced magnetic resonance imaging in five hundred seventy-two patients with known or suspected liver lesions. *Invest Radiol*. 2009 Mar;44(3):168-76. PMID: 19169143
150. Bredart A, Kop JL, Fall M, et al. Perception of care and experience of examination in women at risk of breast cancer undergoing intensive surveillance by standard imaging with or without MR. *Patient Educ Couns*. 2012 Mar;86(3):405-13. PMID: 21795009
151. Chang Y, Lee GH, Kim TJ, et al. Toxicity of magnetic resonance imaging agents: small molecule and nanoparticle. *Curr Top Med Chem*. 2013;13(4):434-45. PMID: 23432006
152. American College of Radiology. ACR manual on contrast media [version 9]. Reston (VA): American College of Radiology; 2013. 128 p.
153. Thomsen HS. Nephrogenic systemic fibrosis. *Imaging Decis*. 2008 Mar 21;11(4):13-18.
154. FDA drug safety communication: new warnings for using Gadolinium-based contrast agents in patients with kidney dysfunction. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2010 Dec 23 [accessed 2013 Jul 29]. [3 p]. Available: <http://www.fda.gov/Drugs/DrugSafety/ucm223966.htm>.

155. Public health advisory - Gadolinium-containing contrast agents for magnetic resonance imaging (MRI). [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2006 Jun 8 [updated 2010 Jun 22]; [accessed 2013 Jul 29]. [2 p]. Available: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/PublicHealthAdvisories/ucm053112.htm>.
156. FDA requests boxed warning for contrast agents used to improve MRI images. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2007 May 23 [updated 2013 Apr 10]; [accessed 2013 Jul 29]. [2 p]. Available: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108919.htm>.
157. Harinck F, Nagtegaal T, Kluijdt I, et al. Feasibility of a pancreatic cancer surveillance program from a psychological point of view. *Genet Med*. 2011 Dec;13(12):1015-24. PMID: 21857231
158. Vasen HF, Wasser M, van Mil A, et al. Magnetic resonance imaging surveillance detects early-stage pancreatic cancer in carriers of a p16-Leiden mutation. *Gastroenterology*. 2011 Mar;140(3):850-6. PMID: 21129377
159. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol*. 2006 Jun;4(6):766-81.
160. Canto MI, Hruban RH, Fishman EK, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology*. 2012 Apr;142(4):796-804; quiz e14-5. PMID: 22245846
161. Verna EC, Hwang C, Stevens PD, et al. Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. *Clin Cancer Res*. 2010 Oct 15;16(20):5028-37. PMID: 20876795
162. Al-Sukhni W, Borgida A, Rothenmund H, et al. Screening for pancreatic cancer in a high-risk cohort: an eight-year experience. *J Gastrointest Surg*. 2012 Apr;16(4):771-83. PMID: 22127781
163. Langer P, Kann PH, Fendrich V, et al. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut*. 2009 Oct;58(10):1410-8. PMID: 19470496
164. Wang KX, Ben QW, Jin ZD, et al. Assessment of morbidity and mortality associated with EUS-guided FNA: a systematic review. *Gastrointest Endosc*. 2011 Feb;73(2):283-90.
165. Bilimoria KY, Bentrem DJ, Tomlinson JS, et al. Quality of pancreatic cancer care at Veterans Administration compared with non-Veterans Administration hospitals. *Am J Surg*. 2007 Nov;194(5):588-93. PMID: 17936418
166. Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for determining research gaps during systematic reviews. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2011 Jun. 79 p. (Methods future research needs report; no. 2). Also available: http://www.effectivehealthcare.ahrq.gov/ehc/products/201/735/FRN2_Frameworks_2011_0726.pdf.
167. Puli SR, Bechtold ML, Buxbaum JL, et al. How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass?: a meta-analysis and systematic review. *Pancreas*. 2013 Jan;42(1):20-6. PMID: 23254913
168. Zhao WY, Luo M, Sun YW, et al. Computed tomography in diagnosing vascular invasion in pancreatic and periampullary cancers: a systematic review and meta-analysis. *Hepatobiliary Pancreat Dis Int*. 2009 Oct;8(5):457-64. PMID: 19822487
169. Hartwig W, Schneider L, Diener MK, et al. Preoperative tissue diagnosis for tumours of the pancreas. *Br J Surg*. 2009 Jan;96(1):5-20. PMID: 19016272

170. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med*. 1998 Apr 30;17(8):857-72. PMID: 9595616
171. Song TJ, Kim JH, Lee SS, et al. The prospective randomized, controlled trial of endoscopic ultrasound-guided fine-needle aspiration using 22G and 19G aspiration needles for solid pancreatic or peripancreatic masses. *Am J Gastroenterol*. 2010 Aug;105(8):1739-45. PMID: 20216532
172. Wakatsuki T, Irisawa A, Bhutani MS, et al. Comparative study of diagnostic value of cytologic sampling by endoscopic ultrasonography-guided fine-needle aspiration and that by endoscopic retrograde pancreatography for the management of pancreatic mass without biliary stricture. *J Gastroenterol Hepatol*. 2005 Nov;20(11):1707-11. PMID: 16246190
173. Brune K, Abe T, Canto M, et al. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. *Am J Surg Pathol*. 2006 Sep;30(9):1067-76.
174. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7:10. PMID: 17302989

Abbreviations and Acronyms

95 percent CI:	95 percent confidence interval
ACR:	American College of Radiology
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
IV:	intravenous
kg:	kilogram
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.³⁶