Evidence report for surgery vs. watchful waiting for branch-duct intraductal papillary mucinous neoplasm (BD-IPMN)

Prepared by EBSCO Health Innovations and EBM Development Department:

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Brian S. Alper, MD, MSPH, FAAFP, FAMIA, Chief Medical Knowledge Officer

Table of Contents

*Note that each *section* of the report also has *section-specific* page numbering at the bottom-right corner of the page. The above page numbers refer to the *report-specific* page number, which appears in bolded and italicized font in the top-right corner of the page.

Evidence report for surgery vs. watchful waiting for branch-duct intraductal papillary mucinous neoplasm (BD-IPMN)

Scoping

EBSCO Information Services

March 3, 2020

Prepared by EBSCO Health Innovations and EBM Development Department:

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Brian S. Alper, MD, MSPH, FAAFP, FAMIA, Chief Medical Knowledge Officer

Abbreviations

General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IQR – interquartile range
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NMA – network meta-analysis
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SD – standard deviation
SE – standard error
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

Abbreviations specific to this report that may appear in this report

BD-IPMN – branch duct intraductal papillary mucinous neoplasm
ERCP – endoscopic retrograde cholangiopancreatography
ESGCTP – European Study Group on Cystic Tumours of the Pancreas
EUS – endoscopic ultrasound
IPMN – intraductal papillary mucinous neoplasm
MD-IPMN – main duct intraductal papillary mucinous neoplasm
MPD – main pancreatic duct
MRCP – magnetic resonance cholangiopancreatography
MRI – magnetic resonance imaging
MT-IPMN – mixed type intraductal papillary mucinous neoplasm

Methods

Using an established, structured template that delineates key elements for scoping (i.e., the population, interventions, and key outcomes to consider), we collaboratively agreed with UKSH on the scope of the present evidence report. Scoping was completed on March 3, 2020.

Where outcomes will be answered with systematic searches, critical appraisal, and evidence synthesis, we will state the intended approach after we state the outcome(s) of interest for that FAQ. For example, we might say: "The outcome of interest is all-cause mortality. We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist or meta-analysis is not the most appropriate method of synthesis." Otherwise, where we say: "We will include a description of", "We will include descriptive responses", or something similar, we will answer the FAQ with descriptive responses, which do not involve systematic evidence searches, critical appraisal, or evidence synthesis.

Results – Criteria Selection for Critical Appraisal

Population:

Inclusion and exclusion criteria are based on the 2018 guideline from the ESGCTP. As also noted by the 2018 guideline from the ESGCTP, the inclusion and exclusion criteria highlight "the importance of evaluating for the presence of multiple risk factors. The greater the number of risk factors, the higher the probability of malignancy."

Inclusion criteria

Patients with branch duct IPMN and relative criteria for resection, which are any of:

- growth rate ≥5 mm/year
- increased serum CA 19.9 level >37 units/ml in the absence of jaundice
- main pancreatic duct (MPD) diameter 5 to 9.9 mm
- cyst diameter ≥40 mm
- symptoms (new-onset diabetes mellitus or IPMN-induced acute pancreatitis)
- contrast-enhancing mural nodules <5 mm

Exclusion criteria

Absolute criteria for resection of branch duct IPMN, which are any of:

- presence of jaundice
- cytology positive for high-grade dysplasia or cancer
- contrast-enhancing mural nodule ≥5 mm
- solid mass
- MPD dilatation ≥10 mm

Ineligibility for surgery due to any contraindications or unwillingness for surgery

Intervention and Comparator/Options:

Surgery

The standard surgery is an oncologic resection with lymphadenectomy. The degree to which the pancreas must be resected may vary, up to a full pancreatectomy. Specific surgical techniques may vary depending on the location of the neoplasm and the degree to which the glandular tissue is involved, but parenchyma-sparing pancreatectomy (PSP; a minimally-invasive surgery mainly utilized in pancreatic lesions that are benign or have a very low risk of malignancy) will not be considered relevant.

Watchful waiting

This approach includes regular monitoring with image studies and the potential for surgery later if there are signs of progression.

Outcomes:

For evidence searches in this topic, the 2018 guidelines on pancreatic cystic neoplasms (from the ESGCTP) is based on an extensive systematic literature search conducted between March 2016 and October 2016. The systematic review included randomized or observational cohort studies with at least 20 patients and systematic reviews published in English. However, neither the search terms nor further details about the systematic review are referenced with the guideline. We will therefore use the 265 references cited in the guideline as representative of a systematic review with search date March 2016. We will limit subsequent searches to randomized trials or systematic reviews published after March 2016, guidelines published in 2018 or later, and references shared by subject matter experts.

FAQ 1: What does the treatment involve?

We will include a description of the treatment or procedure, including frequency of monitoring and length of hospital stay as relevant. For the surgical option, we will also include the possibility of needing total pancreatectomy.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 2: Will I live longer?

The outcome of interest is all-cause mortality, preferably expressed as median survival measured in the context of randomized comparisons. If not available for the diverse population of branch duct IPMN with relative indications for surgery, then the question may be handled differently by option: For the group treated with surgery, the postoperative mortality rates may be reported. For the group treated with watchful waiting, cancer-related mortality rates may be reported.

FAQ 3: Will I get cancer?

The outcome of interest is risk for malignant transformation, and this is specific to the watchful waiting option. The risk may vary with different reasons for being in the “relative indication for surgery” group so may be reported as ranges with a comment that risks vary by patient-specific factors.

FAQ 4: How will the treatment affect my quality of life?

The outcome of interest is long-term modifications to lifestyle, such as changes to dietary patterns that may occur with the surgery.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 5: When will I recover?

The outcome of interest is return to usual activities after surgery.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 6: What are the risks?

For the surgery group, the outcomes of interest are intraoperative and postoperative complications that have symptomatic consequences.

For the watchful waiting group, the outcome of interest is risk of cancer as noted in FAQ 3.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018 May;67(5):789-804. PubMed

Evidence report for surgery vs. watchful waiting for branch-duct intraductal papillary mucinous neoplasm (BD-IPMN)

Evidence Synthesis

EBSCO Information Services

April 10, 2020

Prepared by EBSCO Health Innovations and EBM Development Department:

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Brian S. Alper, MD, MSPH, FAAFP, FAMIA, Chief Medical Knowledge Officer

Methods

Where evidence is very limited, or the FAQ is scoped as a descriptive response, such that no evidence synthesis or processing is applied, the descriptive summary/-ies will be given.

For each FAQ for which evidence synthesis or processing is considered, the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis will be summarized in Evidence Review Tables. For each outcome, Evidence Synthesis Process tables will then articulate the method selected for evidence synthesis and justification of that method. We will do this for the effect estimate (i.e., answering the question "Is there a difference between the intervention and comparator?") and results will be presented with GRADE-based certainty of evidence ratings related to the certainty of effect estimates. For FAQs which require noncomparative/option-specific responses (i.e., the FAQ is "What will happen with this option?" rather than "How do things change with this option?") the Evidence Synthesis Process tables will be extended to include the method to produce noncomparative responses.

For summary statements representing a plain language summary of evidence appraisal and synthesis

We will include the following 2 items immediately after the summary statement as a parenthetical, regardless of whether they occur in the Summary of Findings section or the individual FAQs in the body of the Evidence Synthesis document:

- our certainty in the summary statement (categorized as High, Moderate, Low, or Very low), and
- the number and type of studies informing the statement, as well as a label for the studies in "[Author] [Year]" format.

If the study informing the summary statement is a systematic review and meta-analysis, then unless there are compelling reasons to proceed in a different manner, we will cite the systematic review and meta-analysis as the source. We will do this even if the result on which our summary statement is based comes from a subset of studies in that systematic review and meta-analysis (e.g., a meta-analysis of 5 out of 10 studies, because only 5 of the 10 reported on the outcome of interest). If EBSCO Information Services conducts its own meta-analysis of studies to inform a summary statement, we will list the individual studies.

For summary statements representing a plain language summary of descriptive sources

Certainty rating and provision of details about contributing studies do not apply. Accordingly, we will not include a parenthetical at the end of the summary statement. However, when descriptive summaries appear in the Summary of Findings section, we will include a general parenthetical citation of the references we consulted. We will place this at the end of the relevant FAQ in the Summary of Findings section. For summary statements occurring in the body of the Evidence Synthesis document, we will provide this general parenthetical citation as part of the longer descriptive summary component that precedes the simplified summary statement.

Results – Summary of Findings

FAQ 1: What does the treatment involve?

Surgery

You will have surgery to remove some of your pancreas. The pancreas is near other body parts. This includes the spleen, the gallbladder, and parts of the stomach, intestines, and tube that connects the gallbladder to the intestines. Depending on the kind of surgery you have, some of these parts may need to be taken out as well. Sometimes, the whole pancreas has to be removed, but this is not common. Your healthcare team can talk with you more about which surgery might be best for you.

The surgery may take about 2 to 7 hours and you may be in the hospital for 3 to 10 days. This depends on the kind of surgery you have and how healthy you are. You will have pain after surgery, but you will get medicine to help with this. You may be able to have a type of surgery that uses tools and cameras that are passed through smaller cuts to do the surgery. This is called a "laparoscopic" surgery. But this may not be an option for everyone and may not be an option at your hospital. You may have a tube where the surgery was done to help drain fluid. If you have a tube, it may come out within a few days or may stay in for a while after you leave the hospital.

After surgery, you will keep having follow-up visits to monitor how you are doing. These visits will sometimes include having tests to get pictures of the pancreas. You and your healthcare team can discuss how often these visits and tests should occur. If things stay the same during your visits and tests, your healthcare team may increase the time between your visits and tests.

Watchful waiting

Your healthcare team will monitor the IPMN with follow-up visits and pictures of your pancreas. They may also want to get blood tests. You and your healthcare team can discuss how often these visits and tests should occur. If things stay the same during your visits and tests, your healthcare team may increase the time between your visits and tests.

(Sources consulted for these descriptive responses include ACS 2019, Andrén-Sandberg 2011, Bishop 2011, Buscail 2019, Columbia University nd, Elta 2018, ESGCTP 2018, Faitot 2015, Goudard 2014, Hackert 2015, Ho 2005, Johns Hopkins nd, Mayo Clinic 2019, Memorial Sloan Kettering Cancer Center 2017 – 2018, MyHealth Alberta 2019, NIH 2019, USCF nd)

FAQ 2: What is my chance of dying?

Surgery

If using the point estimate

The risk of dying from the surgery may go down as a hospital is more and more used to doing the surgery. Out of 100 people having the surgery at a hospital that is very good at doing the surgery, about 2 (2%) may die from the surgery. This number may be higher for other hospitals.

(Very low certainty; based on 1 systematic review [Scheiman 2015])

If using the confidence interval

The risk of dying from the surgery may go down as a hospital is more and more used to doing the surgery. Out of 100 people having the surgery at a hospital that is very good at doing the surgery, 1 to 3 (1% to 3%) may die from the surgery. This number may be higher for other hospitals.

(Very low certainty; based on 1 systematic review [Scheiman 2015])

Watchful waiting

Out of 100 patients who have watchful waiting:

- 1 (1%) may die of cancer within 3 years
- 2 to 3 (2% to 3%) may die of cancer within 5 years

(Moderate certainty; based on 1 cohort study [Crippa 2017])

FAQ 3: Will I get cancer?

Surgery

Although surgery will remove the IPMN and lower your risk of getting cancer, some people may get another IPMN later. This is why you still need follow-up visits and tests after having surgery. While some IPMNs turn into cancer, not all IPMNs do this (see the answer to this question for the 'Watchful waiting' option). If you get another IPMN, you may need to decide again whether you want to have surgery or watch it.

(See FAQ 1 for references)

Watchful waiting

Out of 100 patients who have watchful waiting:

- 3 (3%) may get pancreatic cancer within 3 years
- 7 (7%) may get pancreatic cancer within 5 years

(Low certainty; based on 1 cohort study [Uehara 2008] with results that are broadly consistent with 1 systematic review that has more indirectness [Choi 2017])

FAQ 4: How will the treatment affect my quality of life?

Surgery

The surgery can make your intestines slow down, so you will return to eating slowly after you have surgery. Early on, you will have mostly liquids. Many people can eat at least some food within 2 or 3 days after surgery, but this takes longer in some people. Your healthcare team may suggest eating smaller meals more often during the day while your intestines recover. This may take several weeks. Even after you recover, you may still find that you cannot eat or drink as much as you could before the surgery. Some people also find that certain foods or drinks give them an upset stomach. You may be able to take medicine to help with this. You will also have regular follow-up visits and tests (see "What does the treatment involve?"). If your whole pancreas is removed, you will have to change the way you eat and take medicine for the rest of your life, including insulin. This is because your body needs insulin to control your blood sugar, and insulin is usually made by your pancreas. If your spleen is removed, you may take antibiotics for a while after the surgery.

Watchful waiting

You will have regular follow-up visits and tests (see "What does the treatment involve?"). Some people might worry from time to time about watching the IPMN instead of removing it.

(See FAQ 1 for references consulted for these descriptive responses)

FAQ 5: When will I recover?

Surgery

It is normal to feel tired after the surgery. Recovering from a major surgery takes time. The way you eat and drink may need to change, at least for a while (see "How will the treatment affect my quality of life?"). You may return to driving within 2 to 3 weeks. It may take 4 to 8 weeks for you to get back to doing all the things you normally do, including work. You can discuss timing specific to you with your healthcare team.

Watchful waiting

Does not apply (this FAQ is scoped only for the option of watchful waiting)

(See FAQ 1 for references consulted for these descriptive responses)

FAQ 6: What are the risks?

Surgery

Out of 100 people having surgery, 25 to 35 (25% to 35%) may have a problem with the surgery. Risks may depend on the kind of surgery you have and the hospital where you have the surgery. Problems may include:

- infection
- bleeding
- blood clot
- your stomach or intestines slowing down too much or for too long
- fluids from your pancreas, liver, or gallbladder leaking inside you
- having a connection between your pancreas and some other body part that is not normal (often called a “fistula”)
- dumping syndrome, which can make you feel sweaty, shaky, dizzy, tired, weak, and flushed and give you a headache and fast heart rate

See “What is my chance of dying?” for the risk of dying due to the surgery.

Watchful waiting

The risk with watchful waiting is the risk the IPMN will become a cancer. See “Will I get cancer?”.

(See FAQ 1 for references consulted for these descriptive responses; also informing this FAQ is Scheiman 2015 for the risk of surgical complication/post-surgical morbidity)

Search Summary

Number of articles screened and selected

	Screened	Selected*
1st-round (Citation tracing from 2018 guideline from the ESGCTP)	265	1†
2nd-round (DynaMed)	21	1
3rd-round (Systematic review searches)	20	1
4th-round (Original article searches)	2	0
5th-round (Citation tracing from other sources)	1‡	1‡
Total	*309*‡	*4*‡

* Number shown is after deduplication

† Other references were not relevant for this evidence report (see Search and Selection for details)

‡ Does not include 9 citations in Choi 2017 for which we reviewed full text to assess representativeness

	Articles selected for evaluation (Author Year)
Systematic reviews	2 (Choi 2017, Scheiman 2015)
Randomized, controlled trials	0
Other article types	2 (Crippa 2017 [multicenter cohort study], Elta 2018 [guideline]*)

*Elta 2018 was only used for citation tracing to supplement citation tracing of the 2018 ESGCTP guideline. Citation tracing of Elta 2018 yielded the systematic review Scheiman 2015 (which provides data on surgery-related mortality). Therefore, Elta 2018 does not appear in subsequent parts of this evidence report.

Results – Synthesis Details

FAQ 1: What does the treatment involve?

Surgery

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

As noted in Scoping, the standard surgery is an oncologic resection with lymphadenectomy. The degree to which the pancreas will need to be resected and specific surgical techniques may vary depending on the location of the neoplasm and the degree to which glandular tissue is involved, but the surgery may involve:

- partial (subtotal) removal of the pancreas
    - a (partial) pancreaticoduodenectomy (commonly called a Whipple procedure), which, in addition to removing the head of the pancreas (sometimes also a portion of the body), also involves removal of the gallbladder and part of the bile duct and stomach (a so-called pylorus-sparing Whipple does not remove a portion of the stomach)
    - a distal pancreatectomy, which, in addition to removing the left side of the pancreas (tail or tail and portion of the body), also often involves splenectomy
- total removal of the pancreas, termed a total pancreatectomy (this is not a common approach for this condition, but it also involves removal of the spleen, gallbladder, and portions of the stomach and small intestines)

Some have also described using enucleation or median/central pancreatectomy (so-called parenchyma-sparing pancreatectomy procedures), but in line with the 2018 ESGCTP guideline, these approaches are not considered here.

Depending on the surgery selected and the complexity of the patient's situation, the surgery may take 2 to 7 hours on average (at least one center reports up to 12 hours for a Whipple depending on a patient's complexity but also gives a lower estimate of 4 hours). Depending on the specifics of the patient and the institution where the surgery is performed, a laparoscopic approach may be an option. How long a patient stays in the hospital can also vary, but patients may stay in the hospital for 3 to 10 days on average (though patients may sometimes need 2 weeks in the hospital). Postoperative pain is to be expected, and a postoperative drain may be required. The drain may be removed relatively soon (e.g., within a few days) or the patient may be discharged with the tubing still in place (to be removed at a follow-up visit). Because the gastrointestinal system slows down in response to the surgery (physiologic ileus), patients will also slowly resume oral intake. Other than basic principles (e.g., progressing from clear liquids to eventually demonstrating tolerance for solids and liquids, and once eating, eating smaller portions more frequently throughout the day) the resumption of oral intake in many ways proceeds in an individualized, trial-and-error manner (e.g., some patients may report intolerance for certain foods while others do perfectly fine with them). Diet is addressed further in FAQ 4 "How will the treatment affect my quality of life?".

Due to the often-multifocal nature of IPMNs and the risk of developing clinically-relevant disease in the remnant pancreas (barring total pancreatectomy), major guidelines recommend ongoing surveillance after surgical resection for as long as the patient remains a surgical candidate and is willing to have surgery if it becomes indicated. However, guidelines note data are lacking to guide surveillance; the timing and nature of the follow-up may vary depending on local institutional standards and the specifics of the patient's case (e.g., degree of dysplasia seen on surgical pathology of the resected specimen). If the patient's situation remains stable (e.g., no important changes during the 1st year of postoperative surveillance), the

interval between follow-up visits and imaging may be reasonably increased. The recommended imaging modality is MRI/MRCP or EUS. Although different guidelines may suggest different approaches to surveillance, we consider here the recommendations of the 2018 ESGCTP guidelines given the role of these guidelines in this evidence report:

- For patients with BD-IPMN who are found to have high-grade dysplasia, the 2018 ESGCTP guidelines recommend follow-up every 6 months for the first 2 years and yearly follow-up thereafter.
- For other patients with BD-IPMN and low-grade dysplasia, the 2018 ESGCTP guidelines recommend follow-up every 6 months for the first year and yearly follow-up thereafter.
- For patients with multiple BD-IPMN who have BD-IPMN remaining in the pancreas after surgery, the 2018 ESGCTP guidelines recommend evaluation of remaining BD-IPMN as would occur for a solitary BD-IPMN (i.e., each BD-IPMN "should be evaluated individually for the presence of features associated with malignancy" and should thus be treated as a "single entity"); accordingly, if the remaining BD-IPMN has a relative indication for surgery but is not resected, the 2018 ESGCTP guidelines recommend follow-up every 6 months.

Per the 2018 ESGCTP guidelines, evaluation at follow-up should include clinical evaluation, serum levels of CA 19.9, and imaging with MRI and/or EUS.

Descriptive Summary Results

You will have surgery to remove some of your pancreas. The pancreas is near other body parts. This includes the spleen, the gallbladder, and parts of the stomach, intestines, and tube that connects the gallbladder to the intestines. Depending on the kind of surgery you have, some of these parts may need to be taken out as well. Sometimes, the whole pancreas has to be removed, but this is not common. Your healthcare team can talk with you more about which surgery might be best for you.

The surgery may take about 2 to 7 hours and you may be in the hospital for 3 to 10 days. This depends on the kind of surgery you have and how healthy you are. You will have pain after surgery, but you will get medicine to help with this. You may be able to have a type of surgery that uses tools and cameras that are passed through smaller cuts to do the surgery. This is called a "laparoscopic" surgery. But this may not be an option for everyone and may not be an option at your hospital. You may have a tube where the surgery was done to help drain fluid. If you have a tube, it may come out within a few days or may stay in for a while after you leave the hospital.

After surgery, you will keep having follow-up visits to monitor how you are doing. These visits will sometimes include having tests to get pictures of the pancreas. You and your healthcare team can discuss how often these visits and tests should occur. If things stay the same during your visits and tests, your healthcare team may increase the time between your visits and tests.

Watchful waiting

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Comparable to the descriptive summary for surgery, data are lacking to determine an ideal strategy for watchful waiting surveillance for the population scoped for this evidence report. However, there is agreement that patients opting not to have surgery should have serial evaluations with some period of regularity. The exact interval between evaluations may be informed by local institutional standards and the specifics of the patient's case (e.g., number and degree of relative indications for surgery). The exact tests utilized in watchful waiting may also vary somewhat, but there is consensus that imaging with MRI/MRCP and/or EUS is considered a cornerstone of surveillance. As with postoperative surveillance, if a patient's situation remains

stable (e.g., no important changes during the 1st year of watchful waiting surveillance), the interval between follow-up visits and imaging may be reasonably increased. As noted above, although different guidelines may suggest different approaches to surveillance, we consider here the recommendations of the 2018 ESGCTP guidelines given the role of these guidelines in this evidence report. They recommend clinical evaluation, serum levels of CA 19.9, and MRI and/or EUS every 6 months if a patient is undergoing watchful waiting.

Descriptive Summary Results

Your healthcare team will monitor the IPMN with follow-up visits and pictures of your pancreas. They may also want to get blood tests. You and your healthcare team can discuss how often these visits and tests should occur. If things stay the same during your visits and tests, your healthcare team may increase the time between your visits and tests.

(ACS 2019, Andrén-Sandberg 2011, Bishop 2011, Buscail 2019, Columbia University nd, Elta 2018, ESGCTP 2018, Faitot 2015, Goudard 2014, Hackert 2015, Ho 2005, Johns Hopkins nd, Mayo Clinic 2019, Memorial Sloan Kettering Cancer Center 2017 – 2018, MyHealth Alberta 2019, NIH 2019, USCF nd)

FAQ 2: What is my chance of dying?

Note: This FAQ was originally scoped as "Will I live longer?". However, we noted in Scoping that if we could not find reasonable measures of all-cause mortality in the context of randomized comparisons that we might handle this question differently by the option. Namely, we stated that for the group treated with surgery, the postoperative mortality rates may be reported and for the group treated with watchful waiting, cancer-related mortality rates may be reported. We are concerned that maintaining the FAQ as "Will I live longer?" in light of the available evidence could be misleading for readers/users of this evidence report, so in Evidence Synthesis, we have changed this to "What is my chance of dying?", and the option-specific answers will give the risk of dying from cancer (with watchful waiting) or from surgery (for the option of surgery).

Surgery

Evidence Review

As noted above, we operationalized this outcome as risk of postoperative mortality for the surgery option.

We identified only 1 source that reported pooled risk of postoperative mortality in patients having surgery for resection of pancreatic cysts, which was a systematic review of the diagnosis and management of pancreatic cysts from the American Gastroenterological Association (Scheiman 2015). This systematic review reported a pooled overall postoperative mortality risk of 2.1% (95% CI 1.5% to 2.7%) in an analysis of 74 studies with 5,484 patients. We share Scheiman 2015's concern that the pooled result may underestimate the true average risk of postoperative mortality, as most studies came from high-volume centers of excellence (where outcomes are likely better) and there is concern for possible publication bias with small studies with no deaths unduly influencing the results. There is also heterogeneity in the estimates, which may be at least partially attributable to the inclusion of different types of cystic lesions of the pancreas (including invasive and non-invasive); for example, the largest study (n = 729) reported a mortality rate of 6.6%, but it also included only people with invasive IPMNs (which may have worse outcomes). Given these issues, we judged the certainty of this pooled estimate to be Very low, with downgrades for indirectness, inconsistency, and publication bias (see Critical Appraisal for additional detail).

Evidence Synthesis Process

Outcome	**Approach taken and justification: option-specific measure**	**Results: option-specific measure**
postoperative mortality	**Meta-analysis already done** (Scheiman 2015), **quantitative expression** This meta-analysis is the only source found for this outcome.	**2.1% (95% CI 1.5% to 2.7%)** Certainty is Very low, with downgrades due to indirectness, inconsistency, and publication bias. We are concerned the pooled estimate may underestimate the true average risk for reasons stated in 'Evidence Review'. However, if applying these findings to centers of excellence, the concern about indirectness would be at least partially assuaged (given the majority of studies are from centers of excellence). One can consider the point estimate or the confidence interval for synthesis. If considering the confidence interval, it may be reasonable to round down and up for the lower and upper bounds, respectively, given the degree of uncertainty in the estimates (e.g., although Scheiman 2015 note concern about publication bias having an attenuating effect, we also noted the largest study contributing to the meta-analytic estimate may have an accentuating effect). We handle the bolded synthesis statement below accordingly.

Evidence Synthesis Results

If using the point estimate

The risk of dying from the surgery may go down as a hospital is more and more used to doing the surgery. Out of 100 people having the surgery at a hospital that is very good at doing the surgery, about 2 (2%) may die from the surgery. This number may be higher for other hospitals. (Very low certainty; based on 1 systematic review [Scheiman 2015])

If using the confidence interval

The risk of dying from the surgery may go down as a hospital is more and more used to doing the surgery. Out of 100 people having the surgery at a hospital that is very good at doing the surgery, 1 to 3 (1% to 3%) may die from the surgery. This number may be higher for other hospitals. (Very low certainty; based on 1 systematic review [Scheiman 2015])

Watchful waiting

Evidence Review

As noted above, we operationalized this outcome as risk of cancer-related mortality for the watchful waiting option.

For this evidence report, our (population) inclusion criterion was patients with BD-IPMN with ≥1 (of 6) relative indication for resection; our exclusion criterion was patients with ≥1 (of 5) absolute indication for resection. This was intended to define a population for whom surgery was not clearly indicated but also not clearly unindicated, and who were therefore suitable candidates for surveillance. As specified in Scoping, we began our searches by using the 265 references from the 2018 ESGCTP guideline, and we limited searches in subsequent rounds to RCTs or systematic reviews published after the search window closure or guidelines published in 2018 or later.

This process identified only 1 surveillance study that reported cancer-related outcome in a population comparable to that which we scoped (Crippa 2017). It was a multicenter, retrospective cohort study that enrolled 281 consecutive patients with BD-IPMN or MD-IPMN (the latter including mixed-type) with 'worrisome features' or 'high-risk stigmata' having non-operative management at 6 centers in the United States, Italy, and France. The Crippa 2017 'worrisome features' were comparable to our scoped 'relative indications' as shown in table below (their 'high-risk stigmata' were roughly comparable to our 'absolute indications').

'Relative indications' listed in the 2018 ESGCTP guideline and 'worrisome features' in Crippa 2017*

Relative indications	Worrisome features
• growth rate ≥5 mm/year • serum CA 19.9 level >37 units/ml in the absence of jaundice • main pancreatic duct (MPD) diameter 5 to 9.9 mm • cyst diameter ≥40 mm • symptoms (new-onset diabetes mellitus or IPMN-induced acute pancreatitis) • contrast-enhancing mural nodule <5 mm	• size >3 cm • MPD size 5 to 9 mm • minor symptoms • pancreatitis • non-enhancing nodules and/or atypical cells at cytology

*The 'worrisome features' specified in Crippa 2017 were introduced in the 2012 updated version of the International Consensus Guidelines for IPMN as a category of risk factors for malignancy for which patients should be followed closely

Crippa 2017 was particularly useful for this evidence report, because it reported outcomes specific to the subgroup of 147 patients with BD-IPMN and ≥1 worrisome feature, which was similar to the population we had scoped (i.e., BD-IPMN patients with a relative indication). The disease-specific survival in this subgroup was 99.2% at 3 years and 97.6% at 5 years. Thus, disease-specific mortality was 0.8% at 3 years and 2.4% at 5 years. We judged certainty as Moderate due to imprecision (small sample size and no reported measure of precision).

Evidence Synthesis Process

Outcome and follow-up	Approach taken and justification: option-specific measure	Results: option-specific measure
disease-specific mortality at 3 and 5 years	**Use results from single study that had population comparable to population scoped, quantitative expression**	**0.8% within 3 years, 2.4% within 5 years** Certainty is Moderate, with downgrade due to imprecision.

Evidence Synthesis Results

Out of 100 patients who have watchful waiting:

- **1 (1%) may die of cancer within 3 years**
- **2 to 3 (2% to 3%) may die of cancer within 5 years**

(Moderate certainty; based on 1 cohort study [Crippa 2017])

FAQ 3: Will I get cancer?

For both options, information about the need for surveillance appears in FAQ 1 “What does the treatment involve?”.

Surgery

Although this question was not scoped for the option of surgery, as noted above (FAQ 1 “What does the treatment involve?”), IPMNs can be multifocal, and there is a possibility of developing disease in the remnant pancreas after surgery (i.e., recurrence); accordingly, a regimen of post-surgical surveillance is recommended by major guidelines, and we explore in some detail the recommendations of the 2018 ESGCTP. We briefly revisit these notions here given the scope of the present FAQ.

Surgery is thought to confer a reduction in risk compared to watchful waiting for the outcome of developing cancer; however, there remains a non-trivial potential for post-surgical recurrence of the BD-IPMN, and this BD-IPMN could then subsequently become cancerous. In a setting where a patient with a BD-IPMN and ≥1 relative indication for surgery elects to have surgery and is subsequently found to have another BD-IPMN with ≥1 relative indication for surgery during his/her post-surgical surveillance, s/he would then conceivably face the same decision as s/he originally faced (in the absence of evidence suggesting his/her recurrence is somehow at higher risk for malignant transformation than the original BD-IPMN). Again, however, although the possibility of multifocality or recurrence underpins the recommendations for ongoing post-surgical surveillance, we will note (1) there remains a possibility of recurrence in the remnant pancreas to make it clear that surgery – absent total pancreatectomy – is not strictly curative per se and (2) that a patient with recurrence may end up facing the decision of pursuing surgery or watchful waiting for a second time.

Descriptive Summary Results

Although surgery will remove the IPMN and lower your risk of getting cancer, some people may get another IPMN later. This is why you still need follow-up visits and tests after having surgery. While some IPMNs turn into cancer, not all IPMNs do this (see the answer to this question for the ‘Watchful waiting’ option). If you get another IPMN, you may need to decide again whether you want to have surgery or watch it.

(See FAQ 1 for references)

Watchful waiting

Evidence Review

As previously noted, our (population) inclusion criterion was patients with branch duct IPMN with ≥1 (of 6) relative indication for resection; our exclusion criterion was patients with ≥1 (of 5) absolute indication for resection. This was intended to define a population for whom surgery was not clearly indicated but also not clearly unindicated. As specified in Scoping, we began our searches by using the 265 references from the 2018 ESGCTP guideline, and we limited searches in subsequent rounds to RCTs or systematic reviews published after the search window closure or guidelines published in 2018 or later. This process identified 1 systematic review that reported progression of IPMNs to cancer that also risk-stratified the IPMNs as part of the systematic review process (Choi 2017). Choi 2017 stratified studies into "low-risk" and "non-low-risk" groups based on patients' risk status. As described in the Choi 2017 summary in Critical Appraisal, the "low-risk" group of studies clearly did not match the population we scoped, because they defined "low-risk" studies as those including patients with lack of MPD dilatation (<5 mm when diameter was specified or a claim of no MPD involvement) and lack of mural nodules, whereas 2 of the relative indications for our scoped population were MPD dilatation (5 to 9.9 mm) and presence of mural nodule (contrast-enhancing, <5 mm). The Choi 2017 "non-low-risk" category was defined as including a population that did not meet their criteria for "low-risk" (i.e., included a non-negligible proportion of patients with MPD ≥ 5 mm or mural nodules). However, we noted that based on the authors' definitions, these "non-low-risk" studies could be comprised of patients at lower *or* higher risk than the intended population for this evidence report. Therefore, we reviewed the "non-low-risk" studies in Choi 2017 to determine how well each represented the desired population. We rated representativeness as High, Moderate, or Low (we include a tabulated description of this evaluation in the Choi 2017 summary in Critical Appraisal). All studies were rated as having Low representativeness except Uehara 2008, which was rated as having Moderate representativeness. Therefore, Uehara 2008 was selected as the most relevant study for outcome extraction.

We rated Uehara 2008 a moderate match for our intended population of BD-IPMN patients with ≥1 (of 6) relative indication for the following reasons:

- all patients had BD-IPMN
  - our Inclusion criteria specified that population has BD-IPMN
- MPD <4 mm in 58% and between 5 and 9 mm in 42% (thus having a sizeable proportion of patients with a relative indication for surgery per MPD dilation)
  - 1 of the 6 relative indications of our inclusion criteria was main pancreatic duct (MPD) diameter 5 to 9.9 mm
- intraductal tumor (mural nodule) <4 mm in 95% and between 5 and 9 mm in 5% (thus most have nodule size constituting a relative indication for surgery)
  - 1 of the 6 relative indications of our inclusion criteria was contrast-enhancing mural nodules <5 mm (although the 2018 ESGCTP guideline also specifies the enhancing nature of the nodule, which is not specified in Uehara 2008)

Cumulative incidence of pancreatic cancer at 3-year and 5-year follow-up time points from most representative individual study (Uehara 2008)

Number of patients	Follow-up time	Cumulative incidence (%)	Certainty (downgrade)
60	3 years	3.1	Low (risk of bias, imprecision)[1, 2]
	5 years	6.9	Low (risk of bias, imprecision)[1, 2]

[1] risk of bias because review authors reported that reporting was unclear about study design (prospective vs. retrospective) and patient enrollment (consecutive vs selective or unclear series)
[2] imprecision due to small sample size (n = 60)

We conclude on only the 3-year and 5-year estimates from Uehara 2008; although a 10-year estimate is provided, we are concerned about the reliability of that estimate given the sample size and average duration of follow-up (mean of 87 months in Uehara 2008). We did not consider the 3- and 5-year pooled estimates from Choi 2017 to be eligible for evidence synthesis statements because we judged them to have Very low certainty because of their risk of bias, imprecision, and indirectness (pooled estimate included populations at higher and lower risk than the population of interest despite being defined as 'non-low-risk'). However, we note that the 3- and 5-year cumulative incidence in Uehara 2008 are at least broadly consistent with the corresponding pooled estimates in Choi 2017 (5.69% [95% CI 1.10% to 12.77%] at 3 years and 9.77% [95% CI 3.04% to 19.27%] at 5 years), which may help assuage concern about the small sample size of Uehara 2008.

Evidence Synthesis Process

Outcome and follow-up (years)	Approach taken and justification: option-specific measure	Results: option-specific measure
development of pancreatic cancer at 3 and 5 years	**Use results from single study that had population comparable to population scoped, quantitative expression** Uehara 2008 is the closest match to the scoped population. As noted in 'Evidence Review', although the study is small, its estimates are at least broadly consistent with the pooled estimates provided by Choi 2017	**3.1% at 3 years, 6.9% at 5 years** Certainty is Low, with downgrades due to risk of bias and imprecision

Evidence Synthesis Results

Out of 100 patients who have watchful waiting:

- **3 (3%) may get pancreatic cancer within 3 years**
- **7 (7%) may get pancreatic cancer within 5 years**

(Low certainty; based on 1 cohort study [Uehara 2008] with results that are broadly consistent with 1 systematic review that has more indirectness [Choi 2017])

FAQ 4: How will the treatment affect my quality of life?

This FAQ was scoped for descriptive summaries surrounding long-term lifestyle modifications that might occur with either option, such as dietary impact. Although this FAQ is intended to focus on long-term impacts, when discussing diet, we address the chronology from postoperative day 1 onward to achieve better flow and to avoid "crowding" of FAQ 1 ("What does the treatment involve?").

Surgery

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Patients will need time to recover (see FAQ 5 "When will I recover?"). If the patient requires splenectomy, s/he may be at greater risk for certain kinds of infections (e.g., encapsulated bacteria), and some may recommend that the patient take prophylactic antibiotics for a while after splenectomy. If the patient has a total pancreatectomy (which is uncommon), s/he will have post-pancreatectomy, insulin-dependent diabetes mellitus, which requires lifelong insulin. Pancreatic enzyme replacement will also be necessary. Some patients with subtotal pancreatectomy may still try digestive enzymes if they experience prolonged indigestion. Many patients experience nausea, vomiting, and/or heartburn after they have surgery on their pancreas. This is often due to gastric ileus in the initial phases of recovery (e.g., see FAQ 1 "What does the treatment involve?"), but even after a patient demonstrates tolerance for solids and liquids prior to hospital discharge, s/he may still have difficulty with eating as his/her gastrointestinal system continues to recover over several weeks. As alluded to in FAQ 1 "What does treatment involve?", general advice when recovering from a pancreatic surgery often involves eating smaller and more frequent meals throughout the day. Some people ultimately make long-term or permanent changes to the way they eat (amount, frequency, and/or composition) to avoid gastrointestinal symptoms.

Descriptive Summary Results

The surgery can make your intestines slow down, so you will return to eating slowly after you have surgery. Early on, you will have mostly liquids. Many people can eat at least some food within 2 or 3 days after surgery, but this takes longer in some people. Your healthcare team may suggest eating smaller meals more often during the day while your intestines recover. This may take several weeks. Even after you recover, you may still find that you cannot eat or drink as much as you could before the surgery. Some people also find that certain foods or drinks give them an upset stomach. You may be able to take medicine to help with this. You will also have regular follow-up visits and tests (see "What does the treatment involve?"). If your whole pancreas is removed, you will have to change the way you eat and take medicine for the rest of your life, including insulin. This is because your body needs insulin to control your blood sugar, and insulin is usually made by your pancreas. If your spleen is removed, you may take antibiotics for a while after the surgery.

Watchful waiting

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Aside from needing lifelong surveillance (as long as the person remains a surgical candidate and is willing to have surgery if it became indicated) and the potential worry some people might have regarding watching the IPMN rather than resecting it, there are no long-term modifications to lifestyle with the option of watchful waiting.

Descriptive Summary Results

You will have regular follow-up visits and tests (see "What does the treatment involve?"). Some people might worry from time to time about watching the IPMN instead of removing it.

(See FAQ 1 for references)

FAQ 5: When will I recover?

Surgery

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Having any of the surgeries noted above (see FAQ 1 "What does the treatment involve?") is a major surgery. It is very normal for people to feel fatigued after the surgery, and it may take 4 to 8 weeks on average for people to resume normal activities. Although the timing of return to activities should be individualized in consultation with the patient's healthcare team (e.g., patients with desk jobs may return to work much earlier than patients with manual labor jobs), general timelines may include returning to driving within 2 to 3 weeks, returning to lifting heavy items within 4 to 8 weeks, and returning to work within 4 to 8 weeks. General concepts concerning dietary "recovery" are addressed above (see FAQ 4 "How will the treatment affect my quality of life?").

Descriptive Summary Results

It is normal to feel tired after the surgery. Recovering from a major surgery takes time. The way you eat and drink may need to change, at least for a while (see "How will the treatment affect my quality of life?"). You may return to driving within 2 to 3 weeks. It may take 4 to 8 weeks for you to get back to doing all the things you normally do, including work. You can discuss timing specific to you with your healthcare team.

Watchful waiting

Does not apply (this FAQ is scoped only for the option of watchful waiting)

(See FAQ 1 for references)

FAQ 6: What are the risks?

Surgery

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Risks may depend, at least in some part, on the extent of the surgery (e.g., more extensive surgery may carry more risk). Standard risks of major surgery apply, such as bleeding, blot clots, and infection. Additionally, patients can experience: prolonged ileus or delayed gastric emptying (beyond the normal physiologic ileus that occurs after abdominal surgery), duct injury/leak or anastomotic leak, pancreatic fistula, and dumping syndrome (also called rapid gastric emptying and associated with various autonomic symptoms, such as feeling sweaty, shaky, lightheaded, tired, weak, and flushed, headache, and palpitations; this is managed with dietary manipulation and, if necessary, medication). Some patients may also experience transient diabetes/glucose intolerance. Permanent diabetes from total pancreatectomy is not a risk of surgery; it is a guarantee and is addressed in FAQ 1: "What does the treatment involve?" and FAQ 4: "How will the treatment impact my quality of life?". Although not scoped for formal evidence review with systematic evidence searches, critical appraisal, and evidence synthesis, we note that the Scheiman 2015 systematic review (which also provided data for the outcome of post-surgical mortality reported in FAQ 2) also reports on post-surgical morbidity. They report substantial variation in the reported risks of post-surgical morbidity/complication, even though they attempted to limit to major events whenever possible. Although they do not include a forest plot for their analysis, their meta-analytic estimate (under a random-effects model) for post-surgical morbidity/complication is 30% (95% CI 25% to 35%). In an attempt to account for some of the variability reported by Scheiman 2015, we use the bounds of the 95% CI in the bolded statements below.

Descriptive Summary Results

Out of 100 people having surgery, 25 to 35 (25% to 35%) may have a problem with the surgery. Risks may depend on the kind of surgery you have and the hospital where you have the surgery. Problems may include:

- **infection**
- **bleeding**
- **blood clot**
- **your stomach or intestines slowing down too much or for too long**
- **fluids from your pancreas, liver, or gallbladder leaking inside you**
- **having a connection between your pancreas and some other body part that is not normal (often called a "fistula")**
- **dumping syndrome, which can make you feel sweaty, shaky, dizzy, tired, weak, and flushed and give you a headache and fast heart rate**

See "What is my chance of dying?" for the risk of dying due to the surgery.

Watchful waiting

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

The risk with watchful waiting is the risk that the IPMN will progress to malignancy (see FAQ 3: "Will I get cancer?").

Descriptive Summary Results

The risk with watchful waiting is the risk the IPMN will become a cancer. See "Will I get cancer?".

(See FAQ 1 for references; also informing this FAQ is Scheiman 2015 for the risk of surgical complication/post-surgical morbidity)

Evidence report for surgery vs. watchful waiting for branch duct intraductal papillary mucinous neoplasm (BD-IPMN)

Search and Selection

EBSCO Information Services

April 10, 2020

Prepared by EBSCO Health Innovations and EBM Development Department:

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Brian S. Alper, MD, MSPH, FAAFP, FAMIA, Chief Medical Knowledge Officer

Methods

In accordance with Scoping, our search and selection process began with examining the 265 references from the 2018 guideline from the ESGCTP. Subsequent searching was limited to randomized trials or systematic reviews published after March 2016, guidelines published in 2018 or later, and references shared by subject matter experts. Thus, examination of the 2018 ESGCTP guideline became first-round searching for this evidence report. The subsequent rounds documented below have each been iterated by 1 to reflect this change from our usual methods (e.g., first-round searching typically starts with DynaMed, but it is considered second-round searching for this evidence report).

Second-round searching will consist of searching DynaMed Plus summaries pertinent to the topic. The search starts with DynaMed Plus because DynaMed Plus content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
>
> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Third-round searching will involve PubMed/MEDLINE® searches for intervention-specific systematic reviews or guidelines that involve a systematic review that are more recent than those identified in first-round searching.

Fourth-round searching will involve searches for original evidence reports. Such searching will be limited to areas considered insufficiently addressed by earlier searches, such as focused concepts published after search dates in systematic reviews.

Fifth-round searching will involve citation tracing from sources found in the preceding rounds of searching. This may be done to identify additional evidence sources if the results from the preceding rounds of searching are insufficient.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

Additional evidence updates may also be added continuously from feedback from any source.

FAQ Summary

Results

First-round searching – citation tracing from 2018 ESGCTP guideline

Source	Tracing	Number of unique references included
ESGCTP 2018	Screening of 265 references forming the guideline	1 (Crippa 2017)

A note about the above process: Although the 2018 ESGCTP guideline included 265 references, relatively few articles warranted full-text screening for the scoped population and outcomes for this evidence report. This is largely due to the comprehensive intent of the guideline, aiming to give clinicians guidance on all matters pertaining to cystic tumors of the pancreas. This includes many areas that are outside of the scope of interest for this evidence report, such as considerable detail on the approach to: diagnostic evaluation; surgical management if surgery is pursued; different types of cystic tumors of the pancreas, such as main duct or mixed-type intrapapillary mucinous neoplasms or mucinous or serous cystic neoplasms; adjuvant or neoadjuvant treatment; and pathology for surgical specimens.

Additionally, although the inclusion and exclusion criteria specified in Scoping are based directly on the 2018 ESGCTP guideline's relative and absolute indications for surgical management, further examination of the references supporting these relative and absolute indications revealed these criteria are based on studies undertaking multivariate analysis of risk factors associated with worse patient-relevant outcomes. However, although this type of analysis can be helpful in identifying independent risk factors, and although relative effect estimates are reported for the multivariate analyses (e.g., odds ratios or hazard ratios for the presence of a given risk factor), these studies did not provide data / estimates that could be used to inform this evidence report.

Consequently, after initial screening and examination of full-text for articles that appeared possibly relevant, only 1 article was ultimately included for this evidence report: Crippa 2017. We include at the end of Search and Selection a table that briefly documents the reasons for excluding studies that may appear (based on abstract review) to meet or possibly meet the eligibility criteria (we limit tabulating exclusion rationale to this subset of studies because tabulating all 265 references would be superfluous).

Second-round searching – DynaMed

DynaMed subsection	Number of article citations	Number of unique references included
Pancreatic Cyst - Approach to the Patient > Management > Considerations according to treatment option > Conservative management	3	1 (Elta 2018)*†
Pancreatic Cyst - Approach to the Patient > Management > Management by type of cyst > Intraductal papillary mucinous neoplasm	2	0*
Pancreatic Cyst - Approach to the Patient > Guidelines and Resources > Guidelines	16	0‡

*2018 guideline from the ESGCTP also in this section.
†Elta 2018 is the 2018 guideline from the American College of Gastroenterology. It was only used for additional citation tracing (see fifth-round searching).
‡2018 guidelines from ESGCTP and American College of Gastroenterology (Elta 2018) also included in this section. Others were published earlier or were not relevant.

Third-round searching – searches for intervention-specific systematic reviews

Database	Search string	Number of search results	Number of unique references included
PubMed April 1, 2020	intraductal papillary mucinous neoplasm AND (watchful waiting OR surveillance OR observation OR surgery OR surgical OR resection) AND systematic[sb] AND ("2016/01/01"[PDAT] : "3000/12/31"[PDAT])	20	1 (Choi 2017)

PARSE mapping

PARSE name	Search string	Number of search results	Number of new references selected for inclusion
EvRep IPMN third round string #1	intraductal papillary mucinous neoplasm AND (watchful waiting OR surveillance OR observation OR surgery OR surgical OR resection) AND systematic[sb] AND ("2016/01/01"[PDAT] : "3000/12/31"[PDAT])	20 (on April 1, 2020)	Not applicable for first run

Fourth-round searching – searches for original evidence reports

Database	Search string	Number of search results	Number of unique references included
PubMed April 1, 2020	intraductal papillary mucinous neoplasm AND (watchful waiting OR surveillance OR observation OR surgery OR surgical OR resection) AND randomized controlled trial[pt] AND ("2016/01/01"[PDAT] : "3000/12/31"[PDAT])	2	0

PARSE mapping

PARSE name	Search string	Number of search results	Number of new references selected for inclusion
EvRep IPMN fourth round string #1	intraductal papillary mucinous neoplasm AND (watchful waiting OR surveillance OR observation OR surgery OR surgical OR resection) AND randomized controlled trial[pt] AND ("2016/01/01"[PDAT] : "3000/12/31"[PDAT])	2 (on April 1, 2020)	Not applicable for first run

Fifth-round searching – citation tracing from other sources

Source	Tracing	Number of unique references included
Elta 2018	Tracing for mortality related to surgery for IPMN	1 (Scheiman 2015)

Search summary:

Number of articles screened and selected

	Screened	Selected*
1st-round (Citation tracing from 2018 guideline from the ESGCTP)	265	1
2nd-round (DynaMed)	21	1
3rd-round (Systematic review searches)	20	1
4th-round (Original article searches)	2	0
5th-round (Citation tracing from other sources)	1†	1†
Total	*309*†	*4*†

* Number shown is after deduplication

† Does not include 9 citations in Choi 2017 for which we reviewed full text to assess representativeness

	Articles selected for evaluation (Author Year)
Systematic reviews	2 (Choi 2017, Scheiman 2015)
Randomized, controlled trials	0
Other article types	2 (Crippa 2017 [multicenter cohort study], Elta 2018 [guideline]*)

*Elta 2018 was only used for citation tracing to supplement citation tracing of the 2018 ESGCTP guideline. Citation tracing of Elta 2018 yielded the systematic review Scheiman 2015 (which provides data on surgery-related mortality). Therefore, Elta 2018 does not appear in subsequent parts of this evidence report.

Characteristics of excluded studies

The list of excluded studies included in table below covers studies that may on the surface appear to meet the eligibility criteria based on initial abstract review but based on full text review were determined to be ineligible.

Study	Reason for exclusion
Han 2018	patients in this study appear to be at lower risk than the intended population for our Evidence Report, and scoped outcomes not reported
Lafemina 2013	patients in this study appear to not match the risk of the intended population for our Evidence Report, and although study reports overall survival which is one of our scoped outcomes it may be driven by competing risks for death
Lawrence 2017	patients in this study had all cyst types (not restricted to IPMN, let alone BD-IPMN), and additionally characteristics of the cysts suggest included patients were at lower risk than the intended population for our Evidence Report
Marchegiani 2015	scoped outcomes not reported
Piciucchi 2013	patients in this study included a mix of BD-IPMN and MD-IPMN (21 BD-IPMN and 14 MD-IPMN) and results were not reported separately for BD-IPMN group
Sahora 2013	analysis combined results of observed and treated patients and scoped outcomes not reported
Fritz 2010	scoped outcomes not reported
Del Chiaro 2017	patients in this study (relevant 'Group 1') appear to be at lower risk than the intended population for our Evidence Report
Nguyen 2015	scoped outcomes not reported
Sugiyama 2003	scoped outcomes not reported
Ogawa 2008	scoped outcomes not reported
Shin 2010	scoped outcomes not reported
Abdeljawad 2014	patients with MD-IPMN only
Hackert 2015	patients with MD-IPMN only
Seo 2016	scoped outcomes not reported
Masica 2017	not specific to BD-IPMN patients and scoped outcomes not reported

Evidence report for surgery vs. watchful waiting for intraductal papillary mucinous neoplasm (IPMN)

Critical Appraisal

EBSCO Information Services

April 10, 2020

Prepared by EBSCO Health Innovations and EBM Development Department:

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Brian S. Alper, MD, MSPH, FAAFP, FAMIA, Chief Medical Knowledge Officer

Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (i.e., risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

FAQ Summary

FAQ 1: What does the treatment involve?

FAQ 2: Will I live longer?

FAQ 3: Will I get cancer?

FAQ 4: How will the treatment affect my quality of life?

FAQ 5: When will I recover?

FAQ 6: What are the risks?

Results

Characteristics and Results of Critically Appraised Studies/Sources

CHOI 2017

Choi SH, Park SH, Kim KW, Lee JY, Lee SS. Progression of Unresected Intraductal Papillary Mucinous Neoplasms of the Pancreas to Cancer: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2017 Oct;15(10):1509-1520.e4. doi: 10.1016/j.cgh.2017.03.020. Epub 2017 Mar 22. PubMed

Relevant to FAQ 3

- **Study design:** systematic review of longitudinal observational studies
- **Population:** patients with IPMNs followed without surgery
    - stratified studies into "low-risk" and "non-low-risk" groups based on patients' risk status
        - low-risk studies defined as including patients with lack of MPD dilatation (< 5 mm when diameter was specified) or a claim of no MPD involvement in original study report plus lack of mural nodules
            - low-risk group would clearly be a poor match for the intended population of this evidence report (and can thus be excluded from further consideration here)
        - non-low-risk studies included patients who did not meet the criteria for low-risk (ie, included non-negligible proportion of patients with MPD ≥ 5 mm or patients with MPD involvement)
            - the SR authors' criteria could allow for non-low-risk studies that are comprised of patients at lower *or* higher risk than the intended population for this evidence report
                - we reviewed the "non-low-risk" studies to determine how well they represented the desired population and selected the most relevant study for outcome extraction as further described in 'Other considerations' section below
- **Study inclusion criteria:**
    - reported cumulative incidence of pancreatic cancer during follow-up or provided data in sufficient detail that allowed for calculation of cumulative incidence values
    - published before search window close of November 30, 2016

- **Number of studies:** 9
    - number of studies of non-low risk IPMNs
- **Number of participants:** 825
    - number of patients in 9 studies of non-low risk IPMNs
- **Duration of follow-up:**
    - not reported
    - 87 months (mean) for most representative study (Uehara 2008; confirmed via review of full text)
    - studies that directly reported cumulative incidence presented results at 1-, 3-, 5-, or 10-year follow-up time points, so the review authors extracted cumulative incidence at these follow-up time points
- Results and Certainty

Below are tables specific to the more representative individual study (Uehara 2008) and the pooled analysis of "non-low-risk" studies (Choi 2017). See 'Other considerations' for evaluations of the representativeness of the other studies.

Cumulative incidence of pancreatic cancer at 3-year and 5-year follow-up time points from most representative individual study (Uehara 2008)*

Number of patients	Follow-up time	Cumulative incidence (%)	Certainty (downgrade)
60	3 years	3.1	Low (risk of bias, imprecision)[1, 2]
	5 years	6.9	Low (risk of bias, imprecision)[1, 2]

* Although a 10-year estimate is provided, we did not extract that due to concerns about the reliability of that estimate at that timepoint given the sample size and the mean of 87 months of follow-up
1 risk of bias because review authors reported that reporting was unclear about study design (prospective vs. retrospective) and patient enrollment (consecutive vs selective or unclear series)
2 imprecision due to small sample size (n = 60)

Cumulative incidence of pancreatic cancer at 3-year and 5-year follow-up time points from pooled results of "non-low-risk" studies (Choi 2017)

Follow-up time	Number of studies	Number of patients	Pooled cumulative incidence (%) (95% CI)	Certainty (downgrade)
3 years	8	805	5.69 (1.10 to 12.77)	Very low (risk of bias, imprecision, indirectness [double-downgrade])[1, 2, 3]
5 years	8	805	9.77 (3.04 to 19.27)	Very low (risk of bias, imprecision, indirectness [double-downgrade])[1, 2, 3]

1 risk of bias because no study deemed "non-low-risk" was rated as high-quality
2 imprecision because pooled cumulative incidence has wide range, likely due to inconsistent rates in individual studies
3 indirectness because studies included patient populations at higher or lower risk than our population of interest

- **Other considerations:**
  - This SR stratified patients into "low-risk" and "non-low-risk" groups. However, the operational criteria used to deem a study population "low-risk" was whether participants had an MPD <5 mm or a claim of the study authors of no MPD involvement. Thus, "non-low-risk" consisted of a study including at least some participants with an MPD ≥5 mm or having MPD involvement (however, if only a minority of participants met these criteria, the authors sometimes classified the study as "low-risk"). However, although the "low-risk" group would clearly be a poor match for the intended population of this evidence report (and can thus be excluded from further consideration here), the SR authors' classification of a "non-low-risk" group does not guarantee representativeness for the population specified in Scoping. Indeed, the SR authors' criteria could allow for "non-low-risk" studies that are comprised of patients at lower or

higher risk than the intended population for this evidence report. Accordingly, we reviewed the "non-low-risk" studies to determine how well they represented the desired population. We considered representativeness to be high, moderate, or low. The choice to use a trichotomous system for categorizing representativeness is ultimately arbitrary but mirrors the certainty ratings used by GRADE aside from excluding the category of "Very low". We recognize attempting to ascertain the degree of representativeness is inherently limited by what each study reported (e.g., some studies might report certain risk factors while others do not, and some studies may report descriptive statistics for risk factors in different ways), but it is nevertheless important to review the studies to determine (as much as possible) the degree to which a study is representative of the intended population. Below is a tabulation of our findings – including a brief rationale for each rating – which serve to highlight why we consider Uehara 2008 to be the closest match.

Study (Author Year)	**Representativeness**	**Rationale**
Uehara 2008	Moderate	• Likely moderate match to risk for intended population suggested by: ○ all patients had BD-IPMN ○ MPD <4 mm in 58% and between 5 and 9 mm in 42% (thus having a sizeable proportion of patients with a relative indication for surgery per MPD dilation) ○ Intraductal tumor (mural nodule) <4 mm in 95% and between 5 and 9 mm in 5% (thus most have nodule size constituting a relative indication for surgery, although we note the 2018 ESGCTP guideline also specifies the enhancing nature of the nodule, which is not specified in this study)
Sawai 2010	Low	• Likely lower risk than intended population suggested by: ○ all patients had BP-IPMN ○ 90.3% of patients were asymptomatic ○ median cyst size 18 mm (range 4 mm to 50 mm) ○ mural nodule in 17.5% (median reported as 0 mm with range of 0 mm to 5 mm, but this does not make sense and suggests these figures represent the median size and range for the overall patient sample, not the median size and range among those with a mural nodule; the results text supports this suggestion) ○ median main duct size 3 mm (range 1 mm to 7 mm)
Uehara 2010	Low	• Likely higher risk than intended population suggested by: ○ limited to patients with MD-IPMN (thus not meeting inclusion criteria at all; patients with MD-IPMN are at higher risk than patients with BD-IPMN and are not considered in this evidence report)
Takuma 2011	Low	• Likely higher risk than intended population suggested by: ○ limited to patients with MD-IPMN (thus not meeting inclusion criteria at all; patients with MD-IPMN are at

		higher risk than patients with BD-IPMN and are not considered in this evidence report)
Ohno 2012	Low	• Likely lower risk than intended population suggested by: ○ all patients had BP-IPMN ○ roughly 30% had ≥1 of: cyst diameter ≥30 mm, MPD diameter ≥6 mm, mural nodule ≥5 mm (no further details provided on the extent to which any given risk factor was present) ○ mean cyst size 22.3 mm ± 9.6 mm ○ mean MPD size 2.5 mm ± 1.2 mm ○ mean mural nodule size 1.9 mm ± 1.0 mm
Roch 2014	Low	• Likely higher risk than intended population suggested by: • limited to patients with MD-IPMN or mixed-type IPMN (thus not meeting inclusion criteria at all; patients with MD-IPMN are at higher risk than patients with BD-IPMN and are not considered in this evidence report)
Dorfman 2015 (follow-up report)/Rosenblatt 2015 (initial report)	Low	• Likely lower risk than intended population suggested by: ○ Dorfman 2015 ○ most patients (86.3%) had BP-IPMN ○ index cyst size ○ median 13 mm ○ ≥ 30 mm in 7.6% (10/131) ○ Rosenblatt 2015 noted exclusion of patients with potential high-risk features which were defined as MD or mixed-type IPMN, baseline mural nodules or thickened cyst wall, or initial cyst size ≥ 3 cm
Lawson 2015	Low	• Likely higher risk than intended population suggested by: • relevant analysis combined patients with "worrisome features" (69.2%) and "high-risk stigmata" (30.8%) as an overall “high-risk” group, but “worrisome features” are roughly comparable to the ESGCTP 2018 ‘relative indications’ and ‘high-risk stigmata’ are comparable to its ‘absolute indications’ and we are primarily interested in only patients with ‘relative indications’
Nagata 2016	Low	• Likely higher risk than intended population suggested by: • limited to patients with MD-IPMN (thus not meeting inclusion criteria at all; patients with MD-IPMN are at higher risk than patients with BD-IPMN and are not considered in this evidence report)

CRIPPA 2017
Crippa S, Bassi C, Salvia R, Malleo G, Marchegiani G, Rebours V, Levy P, Partelli S, Suleiman SL, Banks PA, Ahmed N, Chari ST, Fernández-Del Castillo C, Falconi M. Low progression of intraductal papillary mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis. Gut. 2017 Mar;66(3):495-506. PubMed

Relevant to FAQ3

- **Study design:** multicenter, retrospective cohort study
- **Population:** consecutive patients with BD or MD (the latter including mixed) IPMN with worrisome feature or high-risk stigmata having non-operative management at 6 centers in the United States, Italy, and France
    - reasons for non-operative management options were physicians' recommendation, patient preference, or comorbidities precluding surgery
    - results extracted below specific to 147 BD-IPMN patients with worrisome features
    - worrisome features were ≥ 1 of following
        - size > 3 cm
        - MPD size 5–9 mm
        - minor symptoms
        - pancreatitis
        - non-enhancing nodules and/or atypical cells at cytology

- **Number of participants:** 147
        - specific to BD-IPMN patients with worrisome features
        - 281 patients overall, but patients with MD IPMN or BD IPMN with high-risk stigmata not relevant to our question

- **Duration of follow-up:** 51 months median (in the subgroup of 147 patients with BD-IPMN and worrisome features but no high-risk stigmata)

- **Results and certainty:**
    - disease-specific survival in 147 BD-IPMN patients with worrisome feature
        - 99.2% at 3 years
        - 97.6% at 5 years
        - Moderate certainty
            - Downgrades
                - imprecision
                    - small sample size and no reported measure of precision

- **Other considerations:**
    - report also included other data, but it was not extracted because it was not specific to BD-IPMN patients with worrisome feature but no high-risk stigmata or not in scope
    - worrisome features were introduced in the 2012 updated version of the International Consensus Guidelines for IPMN as category of risk factors for malignancy for which patients should be followed closely

ESGCTP 2018
European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018 May;67(5):789-804. PubMed

Relevant to FAQ2, FAQ3
(We include in this summary a brief delineation of the relative and absolute indications for surgery according to the ESGCTP 2018 guidelines given their central role in this evidence report.)

- **Study design:** European guidelines on the management of pancreatic cystic neoplasms
  - joint initiative of the ESGCTP, United European Gastroenterology, European Pancreatic Club, European-African Hepato Pancreato-Biliary Association, European Digestive Surgery, and the European Society of Gastrointestinal Endoscopy
    - included section '4.12 Which are the relative criteria for resection of BD-IPMN?' which we used to determine our Inclusion criteria in scoping (ie, > 1 relative indication)

Absolute and relative indications for surgery in IPMN (ESGCTP 2018, section 4.12)

Relative indications	Absolute indications
• growth rate ≥5 mm/year • serum CA 19.9 level >37 units/ml in the absence of jaundice • main pancreatic duct (MPD) diameter 5 to 9.9 mm • cyst diameter ≥40 mm • symptoms (new-onset diabetes mellitus or IPMN-induced acute pancreatitis) • contrast-enhancing mural nodule <5 mm	• jaundice not explained by another condition • cytology positive for high-grade dysplasia or cancer • contrast-enhancing mural nodule ≥5 mm • solid mass • MPD diameter ≥10 mm

SCHEIMAN 2015
Scheiman JM, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015 Apr;148(4):824-48.e22. PubMed

Relevant to FAQ2

- **Study design:** systematic review of observational studies
  - evidence-based review of the diagnosis and management of pancreatic cysts from American Gastroenterological Association
    - included section 'Postoperative mortality and morbidity for patients undergoing surgery for pancreatic cysts' from which treatment-related mortality estimates in this summary were extracted
- **Population:**
  - patients having surgery for resection of pancreatic cysts

- **Intervention:**
  - surgery for resection of pancreatic cysts

- **Study inclusion criteria:**
  - reported data on mortality and/or morbidity
    - review authors specified that where possible they restricted data to that related to major morbidity events such as formation of pancreatic fistula

- **Number of studies:** 74 studies reported mortality outcome
  - 77 studies reported mortality and/or morbidity outcome
- **Number of participants:** 5,484
- **Duration of follow-up:**

- **Results and Certainty**
  - pooled overall mortality rate related to surgery
    - 2.1 % (95% CI 1.5% to 2.7%) in analysis of 74 studies with 5,484 patients
    - Very low certainty
      - Downgrades
        - indirectness
          - majority of studies from centers of excellence with high volumes of pancreatic surgery where outcomes are likely to be better
          - pooled estimate combines different types of cysts, as well as invasive and non-invasive cysts
            - largest study (Wasif 2010, n = 729) was restricted to patients with “invasive” IPMNs who may be sicker and therefore have worse treatment-related outcomes
            - see additional notes below under ‘inconsistency’
        - publication bias
          - funnel plot asymmetry suggesting publication bias or other small study effects
            - pooled estimate probably under-estimated because driven by small studies with no deaths
        - inconsistency
          - significant heterogeneity between studies in relation to mortality rates
          - mortality rate of 6.6% in largest study (Wasif 2010, n = 729)
            - this study based on analysis of SEER database, which is an authoritative, population-based source for cancer statistics in the United States
            - however, this study was restricted to patients with “invasive” IPMNs who may be sicker and therefore have worse treatment-related outcomes
            - see additional notes above under ‘indirectness’

- Although not an outcome scoped for systematic evidence searches, critical appraisal, or evidence synthesis, we also note Scheiman 2015 found a considerable rate of post-operative morbidity, even with their attempt to limit to "major events".
    - Their meta-analytic estimate (under a random-effects model) for the risk of post-operative morbidity is 30% (95% CI 25% to 35%)
        - They report this estimate has "significant heterogeneity" based on I^2 of 88% (95% CI 85% to 90%), but I^2 is not sufficient by itself to evaluate heterogeneity, perhaps especially for a univariate estimate.
            - However, they also later note "There is substantial variation between study results, and the reasons for this are not clear. Some will relate to different thresholds for the investigators describing an event as a complication or a major complication." This suggests a further evaluation of the individual estimates beyond I^2.
            - They do not provide a forest plot of their results, but they do report basic counts for each study in their Supplementary Table 1.
        - They do not note concern over publication bias or other small study effects like they had for post-operative mortality

Evidence report for surgery vs. watchful waiting for branch-duct intraductal papillary mucinous neoplasm (BD-IPMN)

Reference list

EBSCO Information Services

April 10, 2020

Prepared by EBSCO Health Innovations and EBM Development Department:

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Brian S. Alper, MD, MSPH, FAAFP, FAMIA, Chief Medical Knowledge Officer

ACS 2019
American Cancer Society. Surgery for Pancreatic Cancer. Last reviewed/updated February 11, 2019. Accessed April 9, 2020. Available at https://www.cancer.org/cancer/pancreatic-cancer/treating/surgery.html.

ANDRÉN-SANDBERG 2011
Andrén-Sandberg A. Complications of pancreatic surgery. N Am J Med Sci. 2011 Dec;3(12):531-5. doi: 10.4297/najms.2011.3531. PubMed

BISHOP 2011
Bishop S. Whipple Procedure the Most Common Surgery to Remove Pancreatic Cancer. Mayo Clinic News Network. 2011 Sep. Accessed April 2, 2020. Available at https://newsnetwork.mayoclinic.org/discussion/whipple-procedure-the-most-common-surgery-to-remove-pancreatic-cancer/.

BUSCAIL 2019
Buscail E, Cauvin T, Fernandez B, Buscail C, Marty M, Lapuyade B, Subtil C, Adam JP, Vendrely V, Dabernat S, Laurent C, Chiche L. Intraductal papillary mucinous neoplasms of the pancreas and European guidelines: importance of the surgery type in the decision-making process. BMC Surg. 2019 Aug 22;19(1):115. doi: 10.1186/s12893-019-0580-y. PubMed

CHOI 2017
Choi SH, Park SH, Kim KW, Lee JY, Lee SS. Progression of Unresected Intraductal Papillary Mucinous Neoplasms of the Pancreas to Cancer: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2017 Oct;15(10):1509-1520.e4. doi: 10.1016/j.cgh.2017.03.020. Epub 2017 Mar 22. PubMed

Note: We do not include the references for the individual studies included in this systematic review for which we reviewed full text to evaluate representativeness. See Critical Appraisal for details.

COLUMBIA UNIVERSITY ND
The Pancreas Center of Columbia University Irving Medical Center, Department of Surgery. What to Expect From Your Surgery and Hospital Stay. Date last reviewed/updated not provided. Accessed April 2, 2020. Available at https://columbiasurgery.org/pancreas/what-expect-your-surgery-and-hospital-stay.

The Pancreas Center of Columbia University Irving Medical Center, Department of Surgery. Whipple Procedure (Pancreaticoduodenectomy). Date last reviewed/updated not provided. Accessed April 2, 2020. Available at https://columbiasurgery.org/conditions-and-treatments/whipple-procedure-pancreaticoduodenectomy.

The Pancreas Center of Columbia University Irving Medical Center, Department of Surgery. Pancreatectomy Surgery (Removal of the Pancreas). Date last reviewed/updated not provided. Accessed April 2, 2020. Available at https://columbiasurgery.org/conditions-and-treatments/pancreatectomy-surgery-removal-pancreas.

CRIPPA 2017
Crippa S, Bassi C, Salvia R, Malleo G, Marchegiani G, Rebours V, Levy P, Partelli S, Suleiman SL, Banks PA, Ahmed N, Chari ST, Fernández-Del Castillo C, Falconi M. Low progression of intraductal papillary

mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis. Gut. 2017 Mar;66(3):495-506. PubMed

ELTA 2018
Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. Am J Gastroenterol. 2018 Apr;113(4):464-479. doi: 10.1038/ajg.2018.14. Epub 2018 Feb 27. Review. PubMed

ESGCTP 2018
European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018 May;67(5):789-804. PubMed

Note: We do not include here the references for the individual studies for which we reviewed full text to evaluate eligibility for inclusion in this evidence report. See Search and Selection for details.

FAITOT 2015
Faitot F, Gaujoux S, Barbier L, Novaes M, Dokmak S, Aussilhou B, Couvelard A, Rebours V, Ruszniewski P, Belghiti J, Sauvanet A. Reappraisal of pancreatic enucleations: A single-center experience of 126 procedures. Surgery. 2015 Jul;158(1):201-10. doi: 10.1016/j.surg.2015.03.023. Epub 2015 May 5. PubMed

GOUDARD 2014
Goudard Y, Gaujoux S, Dokmak S, Cros J, Couvelard A, Palazzo M, Ronot M, Vullierme MP, Ruszniewski P, Belghiti J, Sauvanet A. Reappraisal of central pancreatectomy a 12-year single-center experience. JAMA Surg. 2014 Apr;149(4):356-63. doi: 10.1001/jamasurg.2013.4146. Erratum in: JAMA Surg. 2014 May;149(5):421. PubMed

HACKERT 2015
Hackert T, Fritz S, Büchler MW. Main- and Branch-Duct Intraductal Papillary Mucinous Neoplasms: Extent of Surgical Resection. Viszeralmedizin. 2015 Feb;31(1):38-42. doi: 10.1159/000375111. Review. PubMed

HO 2005
Ho CK, Kleeff J, Friess H, Büchler MW. Complications of pancreatic surgery. HPB (Oxford). 2005;7(2):99-108. doi: 10.1080/13651820510028936. PubMed

JOHNS HOPKINS ND
Johns Hopkins, Department of Surgery, Division of Surgical Oncology. Hepato Pancreato Biliary Surgery: Treatments. Date last reviewed/updated not provided. Accessed April 2, 2020. Available at https://www.hopkinsmedicine.org/surgery/specialty-areas/surgical-oncology/hepato-pancreato-biliary/treatments.html.

Johns Hopkins. Pancreatic Cancer Surgery. Date last reviewed/updated not provided. Accessed April 2, 2020. Available at https://www.hopkinsmedicine.org/health/conditions-and-diseases/pancreatic-cancer/pancreatic-cancer-surgery.

Johns Hopkins. Whipple Procedure. Date last reviewed/updated not provided. Accessed April 2, 2020. Available at https://www.hopkinsmedicine.org/health/conditions-and-diseases/pancreatic-cancer/whipple-procedure.

MAYO CLINIC 2019
Mayo Clinic. Whipple procedure. Last reviewed/updated July 11, 2019. Accessed April 2, 2020. Available at https://www.mayoclinic.org/tests-procedures/whipple-procedure/about/pac-20385054.

MEMORIAL SLOAN KETTERING CANCER CENTER 2017 – 2018
Memorial Sloan Kettering Cancer Center. About Your Distal Pancreatectomy. Last reviewed/updated October 31, 2018. Accessed April 2, 2020. Available at https://www.mskcc.org/cancer-care/patient-education/about-your-distal-pancreatectomy.

Memorial Sloan Kettering Cancer Center. About Your Total Pancreatectomy. Last reviewed/updated July 24, 2017. Accessed April 2, 2020. Available at https://www.mskcc.org/cancer-care/patient-education/total-pancreatectomy.

Memorial Sloan Kettering Cancer Center. About Your Whipple Procedure. Last reviewed/updated November 28, 2018. Accessed April 2, 2020. Available at https://www.mskcc.org/cancer-care/patient-education/about-your-whipple-procedure.

Memorial Sloan Kettering Cancer Center. Surgery for Pancreatic Cysts. Date last reviewed/updated not provided. Accessed April 2, 2020. Available at https://www.mskcc.org/cancer-care/types/pancreatic-cysts/treatment/surgery-pancreatic-cysts.

MYHEALTH ALBERTA 2019
MyHealth Alberta (adapted with permission from Healthwise). Pancreatic Cancer Surgery: What to Expect at Home. Last reviewed/updated 2019. Accessed April 6, 2020. Available at https://myhealth.alberta.ca/Health/aftercareinformation/pages/conditions.aspx?hwid=ug3582

NIH 2019
National Institutes of Health, National Institute on Diabetes and Digestive and Kidney Diseases. Definition & Facts for Dumping Syndrome. Last reviewed/updated January 2019. Accessed April 9, 2020. Available at https://www.niddk.nih.gov/health-information/digestive-diseases/dumping-syndrome/definition-facts.

National Institutes of Health, National Institute on Diabetes and Digestive and Kidney Diseases. Symptoms & Causes of Dumping Syndrome. Last reviewed/updated January 2019. Accessed April 9, 2020. Available at https://www.niddk.nih.gov/health-information/digestive-diseases/dumping-syndrome/symptoms-causes.

National Institutes of Health, National Institute on Diabetes and Digestive and Kidney Diseases. Eating, Diet, & Nutrition for Dumping Syndrome. Last reviewed/updated January 2019. Accessed April 9, 2020. Available at https://www.niddk.nih.gov/health-information/digestive-diseases/dumping-syndrome/eating-diet-nutrition.

National Institutes of Health, National Institute on Diabetes and Digestive and Kidney Diseases. Treatment of Dumping Syndrome. Last reviewed/updated January 2019. Accessed April 9, 2020. Available at https://www.niddk.nih.gov/health-information/digestive-diseases/dumping-syndrome/treatment.

SCHEIMAN 2015
Scheiman JM, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015 Apr;148(4):824-48.e22. PubMed

UCSF ND
University of California San Francisco, Surgical Oncology Program, Department of Surgery. Pancreatic Cysts. Date last reviewed/updated not provided. Accessed April 2, 2020. Available at https://surgicaloncology.surgery.ucsf.edu/conditions--procedures/pancreatic-cysts.aspx.