

When to Perform a Pancreatoduodenectomy in the Absence of Positive Histology? A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS)



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PII: S0039-6060(13)00677-6

DOI: [10.1016/j.surg.2013.12.032](https://doi.org/10.1016/j.surg.2013.12.032)

Reference: YMSY 3639

To appear in: *Surgery*

Received Date: 14 December 2013

Accepted Date: 27 December 2013

Please cite this article as: Asbun HJ, Conlon K, Fernandez-Cruz L, Friess H, Shrikhande SV, Adham M, Bassi C, Bockhorn M, Büchler M, Charnley RM, Dervenis C, Fingerhutt A, Gouma DJ, Hartwig W, Imrie C, Izbicki JR, Lillemoe KD, Milicevic M, Montorsi M, Neoptolemos JP, Sandberg AA, Sarr M, Vollmer C, Yeo CJ, Traverso LW, , When to Perform a Pancreatoduodenectomy in the Absence of Positive Histology? A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS), *Surgery* (2014), doi: 10.1016/j.surg.2013.12.032.

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All authors have no financial disclosures and no conflicts of interest to declare.

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Running head: ISGPS consensus statement PD in the absence of histology

Keywords: Pancreatoduodenectomy, pancreaticoduodenectomy, Whipple procedure, pancreatic cancer, absence of histology, histologic diagnosis, pancreatic mass

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ABSTRACT

Background: Pancreatoduodenectomy (PD) provides the best chance for cure in the treatment of patients with localized pancreatic head cancer. In patients with a suspected, clinically resectable pancreatic head malignancy, the need for histologic confirmation prior to proceeding with PD has not historically been required, but still remains controversial.

Methods: An international panel of pancreatic surgeons working in well-known, high-volume centers reviewed the literature and worked together to establish a consensus on when to perform a pancreatoduodenectomy in the absence of positive histology.

Results: The incidence of benign disease after PD for a presumed malignancy is 5-13%. Diagnosis by ERCP brushings and percutaneous fine needle aspiration (FNA) are highly specific but poorly sensitive. Aspiration biopsy guided by endoscopic ultrasonography (EUS) has greater sensitivity, but it is highly operator-dependent and increases expense. The incidence of autoimmune pancreatitis (AIP) in the benign resected specimens is 30-43%. EUS-guided trucut biopsy, serum levels of IgG4, and HISORt (Histology, Imaging, Serology, Other organ involvement, and Response to therapy) are used for diagnosis. If AIP is suspected but not confirmed, the response to short course of steroids is helpful for diagnosis.

Conclusions: In the presence of a solid mass suspicious for malignancy, consensus was reached that biopsy proof is not required before proceeding with resection. Confirmation of malignancy, however, is mandatory for patients with borderline resectable disease to be treated with neo-adjuvant therapy prior to exploration for resection.. When a diagnosis of AIP is highly suspected, a biopsy is recommended, and a

short course of steroid treatment should be considered if the biopsy does not reveal features suspicious for malignancy

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Introduction

Pancreatoduodenectomy (PD) provides the best chance for a cure in pancreatic head cancer and remains the treatment of choice for suspected pancreatic head and periampullary malignancies. There is general agreement among experienced pancreatic surgeons that histologic confirmation is necessary prior to the start of neoadjuvant therapy, in those with non-resectable locally advanced tumors, or in the presence of metastatic disease. In contrast, however, in patients with a suspected, clinically resectable pancreatic head malignancy, the need for histologic confirmation prior to proceeding with PD remains debatable. It could be argued that biopsy should only be performed in selected cases in which the results will lead to a change in the management of the patient.

Confirming histologic diagnosis was considered more important in the past because of the high peri-operative morbidity and mortality associated with PD. Over the past decade, the need for histologic confirmation prior to resection has become less important as PD has become a much safer procedure and as more sophisticated imaging has allowed for a greater degree of diagnostic accuracy.

Furthermore, issues relating to biopsy-related complications, potential inaccuracy and a false negative result; potential delay in treatment, and risk of tumor seeding, as well as the added cost, must also be taken into account when considering the role of pre-operative biopsy.

Our aim was to develop a consensus statement from a wide range of experts in pancreatic surgery for pancreatic cancer, on the need for an objective, histologic diagnosis of malignancy prior to proceeding with a PD for a patient with a highly suspected pancreatic cancer

Methods

In order to formulate a consensus statement to the question of when to perform a PD in the absence of a positive histology, two medical librarians were consulted. A search strategy was developed to identify potentially relevant studies from the Ovid MEDLINE database. Only articles with English-language abstracts and those published between January 2008 and February 2013 were included. Multiple medical subject headings (MeSH) and Keywords were used including pancreatoduodenectomy, serous cystadenoma, neuroendocrine tumors, chronic pancreatitis and unknown tumors (see Appendix, online version only). All level of evidence was included and rated in descending order: systematic reviews and meta-analyses of randomized controlled trials, prospective, randomized controlled trials, systematic reviews of cohort studies, prospective/retrospective cohort studies, and existing consensus reports, according to the evidence level of individual studies as per the recommendations of the Centre for Evidence-Based Medicine, Oxford, UK (<http://www.cebm.net/>). Only studies published in English were included. Case studies were excluded. References of the included articles were checked to ensure no relevant studies were missed. The search was performed in February 2013.

All relevant literature and a summary of the extracted data were reviewed by the study subgroup (HJA, KC, LF-C, HF, SVS and LWT) of the ISGPS, which resulted in a first draft of the consensus definition and preparation of the statement. During the Consensus Meeting held in Garda/Verona, Italy from April 23rd – 24th, 2013 and attended by members of the ISGPS, the first draft was discussed. A final consensus statement on when to perform a PD in the absence of positive histology was formulated, reviewed by, and agreed by all cosignatories using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.¹

Results

Incidence of benign disease after pancreatoduodenectomy for suspected malignancy

The incidence of benign disease found on pathologic review after PD for a presumed malignancy is reported as 5-13%.¹⁻⁷ Chronic pancreatitis (many of which probably were autoimmune pancreatitis [AIP]) was present in the majority of these benign specimens and appears to be the main associated diagnosis (Level 4) (Figure 1).^{1, 3, 5} By contrast, 5-9% of patients operated on for chronic pancreatitis will show malignancy in the final pathologic examination of the resected pancreas (Table 1).

Preoperative biopsy – The suspicious solid mass

Improvements in cross sectional imaging over the past decade have markedly aided in the differentiation of pancreatic masses. Current computer tomography (CT) and magnetic resonance imaging (MRI) with diffusion sequences are helpful in better characterizing both solid and cystic pancreatic lesions. Still, when reexamining benign lesions resected by a PD that were preoperatively presumed to be malignant, CT, MRI, endoscopic ultrasonography (EUS), and endoscopic cholangiopancreatography (ERCP) imaging had a high false positive rate.⁴

In the past, ERCP brushings have been traditionally obtained in an attempt to obtain an objective diagnosis. The cytologic diagnosis obtained by brushing in malignant biliary strictures, however, is highly specific but poorly sensitive. An overall sensitivity of 33%-54%, a specificity of 90-100%, and an accuracy of only 43%-75% is reported for biliary brushings in pancreatobiliary malignancy^{8,9} One advantage of this approach is that biliary brushing can be done at the time of placement of an endobiliary stent, and therefore, is the preferred initial modality when a stent is being placed for patients with unresectable disease or undergoing neo-adjuvant therapy. Nonetheless, the above results suggest that if neither an endobiliary stent or ERCP are necessary, ERCP brushings may not be indicated nor warranted in the presence of a suspicious lesion that is considered surgically resectable.

Percutaneous fine needle aspiration (FNA) has an accuracy ranging from 61-98% with a high specificity but a relatively low sensitivity. The negative predictive value of percutaneous FNA is reported at about 58% with a range of 23-100%.¹⁰ Large volume pancreas centers do not favor percutaneous biopsies as the first line of diagnosis, and

most experts would not order such a biopsy. In addition to the low sensitivity and predictive value, there is also concern regarding the potential for seeding of the needle tract when performing percutaneous FNA for the diagnosis of a possible pancreatic malignancy¹¹.

EUS-guided FNA (EUS-FNA) is a safe procedure that has been shown to have a clinical utility in the management of both solid and cystic pancreatic lesions. EUS performed by experienced operators permits high-resolution imaging with simultaneous sampling of cyst fluid for cytology, tumor markers, biochemical analysis, and detection of mucin by FNA.

EUS-FNA is reported to have a greater sensitivity than ERCP brushings or percutaneous biopsy in identifying pancreatic cancer, particularly for smaller lesions and minimizes the potential risk of needle seeding of the tract (Level 3b and Level 4).^{1, 4, 10, 12, 13} In multiple reports, however, the negative predictive value of EUS-FNA had a wide range (16-92%). A systematic review of 28 EUS-FNA studies¹⁰ reported a mean negative predictive value of only 72%, while another study⁴ reported a value of only 22% in patients with obstructive jaundice. In other studies, FNA has also been reported as either indeterminate or only suspicious for cancer in over 60% of patients.^{2, 4} Therefore, there remains a substantial subset of patients undergoing EUS-FNA for whom malignancy cannot be excluded without PD. EUS-FNA is also highly operator-dependent and, as with any FNA, the presence of an expert cytopathologist on site is recommended.^{10, 13} This was illustrated in another systematic review of 15 studies with 1860 patients, in which the

pooled sensitivity and specificity of EUS-FNA were 92 % and 96 %; the subgroup analysis of six of these studies with rapid on-site evaluation improved the sensitivity to 95 %¹³

Complications such as hemorrhage, duodenal perforation, acute pancreatitis, infection, or tumor seeding as may occur after percutaneous biopsy¹⁴ are uncommon and occur in 1-5% of patients.

Guidelines of the National Comprehensive Cancer Network (NCCN v1.2013) recommend considering EUS-FNA preoperatively, but these guidelines do not require objective proof of malignancy before operative resection. In one large prospective series, the authors who recommended the routine use of EUS-FNA still advised exploration and resection in patients with clinical and imaging findings that were suspicious for pancreatic cancer, but in whom the EUS-FNA cytology was inconclusive or negative.¹⁵ Increased cost and potential delays in resection are, therefore, a consideration when considering a test that may not alter the decision to explore and resect a mass highly suspicious for an aggressive malignancy.

Other pre-operative studies, such as serum tumor markers (CA19-9,CEA) and positron emission tomography-CT, are useful only when they are positive. When negative, they do not aid in determining the nature of the suspicious lesion and therefore, have little influence in the decision of proceeding with exploration/resection or not. Furthermore, abnormal levels of CA 19-9 can occur often in the presence of obstructive jaundice both in malignant and even benign disease; thus, an increase in serum tumor

markers needs to be interpreted with caution during the decision-making process. In a systematic review, the median sensitivity of serum CA 19-9 levels for diagnosis was 79 (70-90%) and median specificity was 82 (68-91%). As expected, an increase in CA 19-9 levels in non-malignant, jaundiced patients resulted in a decrease in specificity (Level 3a).¹⁶ Some studies have reported that increased serum levels of CA 19-9 above certain levels have correlated with unresectable disease or disease that recurs early in the postoperative period. Per the recommendations of the American Society of Clinical oncology (ASCO), there is general consensus that the use of serum CA 19-9 levels alone is not advocated for determining operability in pancreatic cancer¹⁷

In an environment where cost of delivering care is becoming increasingly more important, adding unwarranted tests and/or procedures prior to operative exploration for a surgically resectable, solid pancreatic mass will result in unnecessary added cost¹⁸

The usefulness of intraoperative frozen section biopsy also remains controversial. Even when frozen section is obtained, the results of the biopsy may not influence the surgeon's decision to proceed with a PD in the presence of high suspicion for a malignant neoplasm.¹⁹ Although Garcea and colleagues suggested that use of intraoperative biopsy and frozen section prevented a pancreatic resection in 35% of patients, the range of false negative rates of intraoperative frozen section is reported to be 7-26%, and for these patients, the discovery of the presence of cancer on permanent section several days later would necessitate reoperation (Level 4 and Level 3b).^{4, 12}

Pancreatitis

In the absence of preoperative histologic confirmation of malignancy, one of the common challenges is differentiating a malignant from an inflammatory mass.¹⁰ Difficulty arises because both pancreatic cancer and chronic pancreatitis (CP) have considerable overlap with regards to clinical presentation and imaging. In this subset of patients, it is important to differentiate CP from AIP.

After PD for a presumed malignancy, the incidence of AIP within the benign specimens is reported to be 30-43%.^{3, 5, 6} This is an important subset of patients to recognize preoperatively before resection, because treatment with steroids is likely to prevent an unnecessary surgical resection.

Two subtypes of AIP have been described: Type 1 - predominantly lobular and Type 2 - predominantly ductal. Type 1 AIP occurs more predominantly in older patients, is most commonly associated with increased levels of serum IgG4 and IgG4-positive plasma cells; type 1 AIP is also easier to diagnose histologically. Type 2 AIP is more prevalent in younger patients, more difficult to diagnose histologically, and less often associated with an increase of serum levels of IgG4.^{5, 20, 21}

EUS-guided trucut biopsy, serum levels of IgG4, and HISORt (Histology, Imaging, Serology, Other organ involvement, and Response to therapy) are used for diagnosis²², but confirming AIP preoperatively can remain a challenge; indeed, in some

series, the incidence of AIP in resected specimens does not appear to have decreased over the past 10 years^{5, 6, 10} despite the increased awareness of the disease. When in doubt, a short term trial with steroids might be the best option to differentiate AIP from a malignant process.²³

In contrast, the presence of chronic pancreatitis is more readily diagnosed preoperatively, but the difficulty involves differentiating if and when a patient with CP develops a malignancy. The International Pancreatitis Study Group cites a risk of developing cancer in CP at 4% over a 20-year period (Level 2a).²⁴ Preoperative differentiation between a mass effect from CP and an actual cancer is often difficult even with the use of state of the art imaging and EUS biopsy.^{2, 10} In contrast to patients with AIP, a PD would be considered an appropriate treatment in the majority of symptomatic patients with CP and the presence of a head mass, even in the absence of malignancy.^{3, 10,}

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Neuroendocrine Neoplasms

The diagnosis of pancreatic neuroendocrine tumors (PNET) is facilitated by the presence of symptoms and identification of the hormonal abnormalities when present; however, 15-40% of PNETs are non-functioning (NF-PNET).^{10, 26} While there is general consensus that the hormonally active PNETs should be treated by resection,^{27, 28} controversy exists regarding the indications for resection of small NF-PNETs.²⁹ Because imaging studies are performed more frequently, the incidental finding of smaller NF-

PNET has become more common. Historically, however, NF-PNETs have usually been large and present at an advanced stage when first diagnosed.²⁸ Survival after resection is affected primarily by the presence of metastases with a median survival of 23 months, compared to 124 and 70 months for those patients with localized or regional disease, respectively.³⁰

Currently, PNETs are being found more frequently with advanced cross sectional imaging. In these patients, histologic confirmation is usually required to confirm that the lesion is a PNET. EUS-FNA is indicated in this subset of patients with suspected PNET and can provide cytological confirmation.^{10 31}

In general, most pancreatic surgeons agree that operative resection is the treatment of choice for NF-PNETs > 2cm or that present rapid growth (> 0.5cm per year). NF-PNETs that are < 2cm are likely to be benign or intermediate-risk lesions; it is reported that only 6% of them are malignant when incidentally discovered.³⁰ In this subgroup of patients, an initial course of non-operative management with close follow-up may be a consideration.

Recent consensus guidelines have been developed for the management of PNETs both in Europe^{27, 30} and North America.²⁸ As such, the consensus of the ISGPS is that an added consensus guidelines statement is not warranted. Furthermore, the indications for operative resection for small PNETs are still in evolution, and real debate exists as to who should or should not be resected, particularly for lesions less than 2 cm

in size. A general background of this subject is included in our consensus statement because of its importance, but we recommend following the consensus guidelines by ENETS and NANETS.

Consensus statements

- In the presence of a solid mass in the head of the pancreas that is suspicious for malignancy, biopsy proof is not required before proceeding with PD when AIP is not suspected (strong recommendation).
- Prior to the beginning of chemotherapy or chemoradiation therapy in patients undergoing neoadjuvant therapy, objective confirmation of malignancy is mandatory (strong recommendation). In these patients, ERCP brushings is preferred in the presence of jaundice, because placement of an endobiliary stent is indicated. Otherwise EUS-FNA is the diagnostic modality of choice (strong recommendation).
- In patients with chronic pancreatitis in whom a malignancy is suspected, resection is indicated even in the absence of histologic proof of malignancy (strong recommendation).
- When a diagnosis of AIP is highly suspected, measurement of serum levels of IgG4 plus a biopsy is recommended (strong recommendation). EUS-guided trucut biopsy is preferred. If biopsy results are not diagnostic or suspicious for

malignancy, a short course of steroid treatment (4-6 weeks) is recommended (qualified recommendation).

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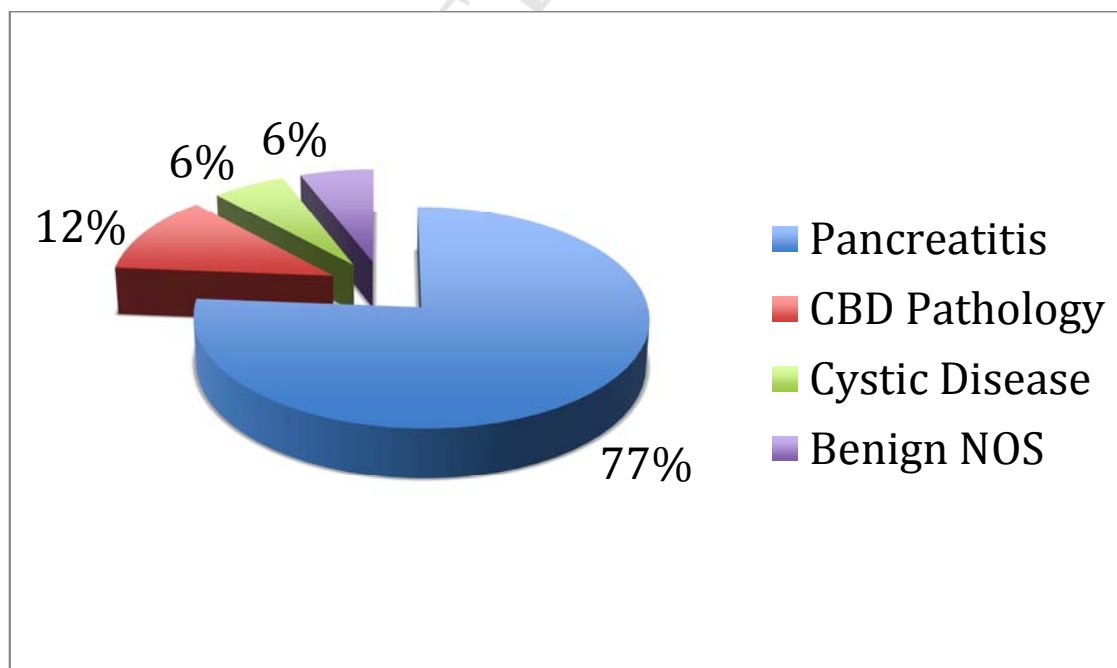
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Table 1. Incidence of Benign Disease Following Pancreatoduodenectomy

Author	Country	Year	Dates of accrual	Number of patients	Non-malignant
Kavanagh	Ireland	2008	1987-2002	112	8
de Castro	Netherlands	2009	1992-2005	639	63
de la Fuente	USA	2010	1992-2007	494	37
Hurtuk	USA	2010	1993-2007	461	45
Manzia	UK	2010	1997-2008	459	49
Van Heerden	Netherlands	2012	2000-2009	274	23
Total				2,439	225

Figure 1. Final diagnosis in benign disease following Pancreatoduodenectomy for suspected malignancy



APPENDIX

1. exp Pancreaticoduodenectomy/
2. Pancreaticoduodenectomy.tw.
3. Pancreatico-duodenectomy.tw.
4. 2 or 3
5. 1 or 4
6. exp Cystadenoma, Serous/
7. exp Neuroendocrine Tumors/
8. (neuroendocrine adj1 tumor*).tw.
9. (serous adj1 cystadenoma).tw.
10. 6 or 9
11. 7 or 8
12. 5 and 10
13. 5 and 11
14. ((suspicious\$ or unknown\$) adj1 tumor\$).tw.
15. exp Neoplasms, Unknown Primary/
16. exp Pancreatitis, Chronic/
17. 14 or 15
18. (chronic adj1 pancreatitis).tw.
19. 16 or 18
20. 5 and 17
21. 5 and 19
22. limit 21 to English language
23. 12 or 13 or 20 or 21
24. limit 23 to English language
25. 23 not 24
26. limit 25 to (abstracts and structured abstracts)
27. 24 or 26
28. limit 27 to yr="2008 -Current"
29. remove duplicates from 28