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Journal

The American Journal of Surgical Pathology, 45(10)

ISSN

0147-5185

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Publication Date

2021-10-01

DOI

10.1097/pas.0000000000001723

Peer reviewed

HHS Public Access

Author manuscript

Am J Surg Pathol. Author manuscript; available in PMC 2022 October 01.

Published in final edited form as:

Am J Surg Pathol. 2021 October 01; 45(10): 1364–1373. doi:10.1097/PAS.0000000000001723.

Towards a More Standardized Approach to Pathologic Reporting of Pancreatoduodenectomy Specimens for Pancreatic Ductal Adenocarcinoma: Cross-continental and Cross-specialty Survey from the Pancreatobiliary Pathology Society Grossing Working Group

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Abstract

In recent literature and international meetings held, it has become clear that there are significant differences regarding the definition of what constitutes as margins and how best to document the pathologic findings in pancreatic ductal adenocarcinoma. To capture the current practice, Pancreatobiliary Pathology Society (PBPS) Grossing Working Group conducted an international multispecialty survey encompassing 25 statements, regarding pathologic examination and reporting of pancreatic ductal adenocarcinoma, particularly in pancreatoduodenectomy specimens. The survey results highlighted several discordances; however, consensus/high concordance was reached for the following: 1) the pancreatic neck margin should be entirely submitted en face, and if tumor on the slide, then it is considered equivalent to R1; 2) uncinate margin should be submitted entirely and perpendicularly sectioned, and tumor distance from the uncinate margin should be reported; 3) all other surfaces (including vascular groove, posterior surface, and anterior surface) should be examined and documented; 4) carcinoma involving separately submitted celiac axis specimen should be staged as pT4. Although no consensus was achieved regarding what constitutes R1 versus R0, most participants agreed that ink on tumor or at and within 1 mm to the tumor is equivalent to R1 only in areas designated as a margin, not surface. In conclusion,

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this survey raises the awareness of the discordances and serves as a starting point towards further standardization of the pancreatoduodenectomy grossing and reporting protocols.

Keywords

pancreatoduodenectomy; pancreatic ductal adenocarcinoma; survey; margin; grossing

INTRODUCTION

The pancreatoduodenectomy often referred to as the eponym Whipple procedure is the most common major surgery to remove tumors of the head of the pancreas, ampulla, distal bile duct, or periampullary duodenum.[1–3] Anatomic complexity of the site where several different structures come together in one small area, combined with the relative rarity of the specimens and lack of familiarity with the organ, render the pancreatoduodenectomy specimens one of the most challenging resection specimens grossed by surgical pathologists.[4–8] A thorough and detailed grossing of the pancreatoduodenectomy specimen is crucial for precise determination of the site of origin of a tumor (ampulla, common bile duct, pancreas, or extra-ampullary duodenum), in conjunction with the proper documentation of areas that the tumor has spread, enables accurate staging and uniform prognostication.[6] However, a lack of a standardized grossing protocol, consensus on the reporting, and the nomenclatures and definitions of margins versus surfaces has raised many debates and questions across specialties, countries, and different practice pathology groups.[4, 7, 9–15]

There are many challenging aspects involving the grossing and reporting of a pancreatoduodenectomy specimen. First, different names are assigned for the same anatomic region in the literature, and in fact, the same name has been used to designate different compartments of the pancreatoduodenectomy as well. For example, the uncinate margin is also known as the retroperitoneal margin or superior mesentery artery (SMA) margin, which can confuse clinicians.[15–21] “Medial margin” was also used by some authors to refer to the uncinate margin.[22, 23] Moreover, the term “posterior margin” is used variably in different guideline texts. Some are referencing only to the uncinate margin itself, while in others, the designation encompasses the entire posterior anatomic region, including the uncinate margin.[24–27] And yet in others, “posterior margin” is limited to the non-uncinate posterior surface of the specimen.[13, 20, 28, 29] There have been debates whether some of the surfaces come off readily, but not resected by the surgeons themselves, should be considered margins or surfaces.[4, 7, 13, 22] Second, different grossing techniques, and margin sectioning methods are used by different institutions leading to a widely variable and incomparable R1 (microscopic residual tumor) resection rate. Furthermore, the extent of sampling (total vs. representative) consequently affects the margin status reporting; modalities using total sampling naturally report a higher frequency of margin positivity.[4, 8, 16, 23, 26, 28, 30] Lastly, the definition of which anatomic regions are to be included in the “margin positivity” (R1), for example, whether the anterior surface is a part of that criteria, has been highly controversial. Additionally, usage of “R1” (margin positivity) has been variable, with some requiring tumor cells to be present on ink as positive, while others qualify carcinoma cells

within 1 mm as R1. Even with the recent changes in the American Joint Commission on Cancer (AJCC) Staging Manual (8th edition) that inarguably defines R1 to be “at or within 1 mm of margin” (≤1 mm); the adoption of this guideline has been variable among practices, and the applicability of this R1 definition to surfaces is still up for debate.[20, 23, 25, 28, 31–33]

In order to capture the current practice patterns and views on these important issues regarding the pancreatoduodenectomy specimen grossing and reporting across specialties and countries, the Pancreatobiliary Pathology Society (PBPS) Grossing Working Group conducted a survey among pathologists, hepatopancreatobiliary surgeons, and oncologists from three geographic regions (Americas, Asia, and Europe). The survey was set out to provoke opinions, especially on 1) the definition of margin versus surface, 2) the definition of R1 versus R0, 3) pathologic reporting issues, and 4) handling of a pancreatoduodenectomy gross specimen specifically in the context of pancreatic ductal adenocarcinoma (PDAC). It is believed that the results will facilitate an appreciation of the current state and hopefully assist the community to better understand the controversial and problematic issues related to pancreatoduodenectomy grossing and reporting towards a goal of resolving these dilemmas and achieving more standardized and applicable protocols.

MATERIALS AND METHODS

The members of the Grossing Working Group (DA, DD, KTJ, GEK, JS), along with input from members of the PBPS Executive Committee (VA, OB), conducted a survey. Before creating a comprehensive survey, an extensive literature review was performed to better understand the controversies on the grossing of pancreatoduodenectomy specimens for PDAC, specifically in grossing protocols, reporting, and staging. These topics had been discussed at the “Pancreas Pathology luncheons” held during the United States and Canadian Academy of Pathology Annual Meetings in 2009, 2012, and 2014, and the proceeding notes of these discussions were utilized to prepare the statements. Based on the most relevant topics identified, a subset of the members constructed the statements that the entire group later discussed. Preliminary results of the survey data were presented at the PBPS Companion Meeting (the United States and Canadian Academy of Pathology 2018 Annual Meeting).

Survey Participants

The survey was prepared not only for pathologists but also for clinicians in other specialties, including surgeons, medical oncologists, and radiation oncologists, who have dedicated expertise in pancreas and PDAC. The survey was sent internationally to these physicians in three geographic regions: Americas (North America and South America), Asia, and Europe. Survey responses received from pathologists included the following countries: Canada, United States of America (USA), Chile, and Mexico (from Americas); India, Japan, and South Korea (from Asia); and Belgium, Ireland, Italy, France, Spain Portugal, Greece, Belarus, Netherlands, Republic of Moldova, Finland, Czech Republic, Russia, Switzerland, Turkey, and United Kingdom (UK) (from Europe). Survey responses received from surgeons included: Canada, Mexico, and the USA (from North America); Japan and South Korea (from Asia); and Italy, Greece, Turkey, and UK (from Europe).

Survey Delivery

A database of physicians with contact information was built with members of the pancreas community, which includes members of the PBPS, Digestive Disease Working Group of the European Society of Pathology (ESP), Gastrointestinal Pathology Working Group of the Spanish Society of Pathology (SEAP), Hepato-Pancreato-Biliary Working Groups of Federation of Turkish Pathologic Societies, The Americas Hepato-Pancreato-Biliary Association (AHPBA), Korean Association of Hepatobiliary Pancreatic Surgery, and Japanese Society of Hepato-Biliary-Pancreatic Surgery. The survey link was emailed to various physicians based on their expertise/interest in the pancreas - pathology, surgery, radiation oncology, and medical oncology. Survey responses from participants, including their country origins, were recorded in the Google Doc survey.

Survey Design

The survey encompassed a total of 25, 24, 23, and 6 statements for pathologists, radiation oncologists, surgeons, and medical oncologists, respectively, related to pancreatoduodenectomy grossing and reporting issues and was often accompanied by anatomic illustrations and graphs for clarification. Each parameter to be surveyed was constructed in a positive statement format rather than an open-ended question. In formulating the statements, an attempt to avoid bias towards either agreement or disagreement was employed. The statements' verbiage was approved by all authors unanimously before incorporated into the survey. All statements were followed by a 5-point Likert scale (strongly agree, agree, neutral, disagree, and strongly disagree),[34, 35] and only one choice was to be selected. Statements were not modified, and data was not discussed with participants. Each participant was blinded to the responses of others to ensure an unbiased opinion.

Survey Data Analyses

A modified version of the Delphic consensus process[36, 37] was used to analyze the responses. For the analysis, "strongly agree" and "agree" were grouped as "agree"; and "strongly disagree" and "disagree" were grouped as "disagree". "Consensus" was defined as equal to or greater than 80% (≥80%) of the responders choosing the same option (agree, neutral, or disagree).[38, 39] "High concordance" was arbitrarily defined as equal to or greater than 75% but less than 80% (≥75% but <80%) responders choosing the same option. Less than 75% (<75%) of responses were considered "no consensus or no high concordance". To calculate and generate tables, Microsoft Excel was used. The differences of opinion among subspecialties and geographic regions (Americas, Asia, and Europe) were also analyzed.

RESULTS

A total of 136 pathologists participated in the survey from a pool of 347 pathologists, a response rate of 39%. Additionally, 73 surgeons participated in the survey. Although an attempt was made to survey radiation oncologists and medical oncologists, the total number of responses was low (1 and 6, respectively); thus, these categories were excluded. Among pathologists, 65 were from the Americas (63 from North America and 2 from Central/South America), 8 were from Asia, and 63 were from Europe. Among surgeons, 24 were from

North America, 43 from Asia, and 6 from Europe. The complete list of survey statements answered by groups (pathologists and surgeons) are provided in Supplementary Table 1.

Of 25 statements for pathologists and 23 statements for surgeons, a consensus was reached for only 7 (28%) statements by pathologists and 7 (30%) statements by surgeons from all three geographic regions (Table 1). An additional 5 (20%) and 2 (8%) statements had high concordance among pathologists and surgeons, bringing the consensus/high-concordance figures to 48.0% and 39.1% for these specialties, respectively. Summarized responses to all statements are included in Table 2. When analyzed by different geographic regions, the frequency of consensus among pathologists was similar (Americas consensus in 10 statements, Asia consensus in 10 statements, and Europe consensus in 11 statements), but not on the same statements. European surgeons had a higher number of responses that reached consensus (16 statements versus 8 for surgeons from the Americas and 10 for Asian surgeons). An in-depth analysis of the survey statements and results per topic is described below.

Margin versus Surface Debate

There was consensus among pathologists (89.0% and 92.6%), and high concordance and consensus among surgeons (79.5% and 86.3%) for the statements defining margin and surface (PS1–2, SS1–2, Table 2). Interestingly, when statements (PS3–7, SS3–7, Table 2) were asked about various specific anatomic areas of the pancreatoduodenectomy specimen, except the uncinate/SMA margin (PS3, SS3, Table 2), there was no consensus about what constitutes a margin by pathologists and surgeons. There was a universal consensus among pathologists and surgeons (92.6% and 90.4%, respectively) that the uncinate margin should be reported as a margin (PS3, SS3, Table 2). Regarding the statement that vascular groove should be reported as a margin (PS4, SS4, Table 2), 65.4% of pathologists and 73.9% of surgeons agreed, although it did not reach consensus. However, regional differences were evident; pathologists from Asia (87.5%) and Europe (82.5%) as well as surgeons from Europe (83.3%) achieved consensus on the issue of designating the vascular groove as a margin statement (PS4, SS4, Table 2). Moreover, Asian surgeons (79.1%) reached high concordance, but only 46.2% of pathologists and 62.5% of surgeons from the Americas considered the vascular groove as a margin. There was also discordance about the posterior and anterior surfaces being considered as margins (PS5–6, SS5–6, Table 2), with only 50.0% of pathologists and 56.2% of surgeons considering the posterior surface as a margin, and 64.0% of pathologists and 42.5% of surgeons actually disagreeing with the statement that the anterior surface should be considered a margin. While most (76.9%) pathologists from the Americas do not consider the anterior surface as a margin, 41.3% of the European pathologists consider the anterior surface as a margin. Only 57.4% of pathologists and 58.9% of surgeons agreed to the statement that it is contradictory to regard the posterior surface of the pancreas but not regard the anterior surface of the pancreas as a margin even though both are not surgically dissected and comes off readily (PS7, SS7, Table 2). Regarding this statement, only American surgeons reached high concordance (79.2%).

Despite the above discordances, there was consensus among the surgeons (89.0%) and high concordance amongst pathologists (78.7%) about reporting the involvement of all free

surfaces (PS8 and SS8), whether they are considered as margin or not, although only 70.8% pathologists from the Americas agreed in comparison to Asian and European pathologists who were in consensus (87.5% and 85.7%, respectively).

Pancreatoduodenectomy Grossing and Reporting

There was consensus that the pancreatic neck margin should be entirely submitted en face, and if the tumor is present, then it is equivalent to R1 (microscopically positive margin) among pathologists (88.2%) and surgeons (93.2%) (PS9, SS9, Table 2). Additionally, the surgeons and pathologists were in consensus (91.8%) and high concordance (79.4%), respectively, that the uncinate/SMA margin should be entirely submitted (PS10, SS10, Table 2). The pathologists also reached consensus (83.1%) and surgeons high concordance (75.3%) to the statement that the tumor distance from the uncinate/SMA margin should be reported, and thus perpendicular sections must be taken (PS11, SS11, Table 2); however, when different geographic regions were analyzed, only 69.8% Asian surgeons agreed. Only pathologists (86.2% and 92.3% for posterior and anterior surfaces, respectively) and surgeons (79.2% for both surfaces) from the Americas reached consensus/high concordance that representative sections of the closest tumor to posterior and anterior pancreatic surfaces are adequate for pathologic assessment (PS15–16, SS14–15, Table 2). There was consensus among pathologists (81.6%) and surgeons (87.7%) that surgeons should mark the resected segment of portal vein/superior mesentery vein (SMV) in order for it to be evaluated by a pathologist (PS22, SS20, Table 2). In summary, there was an overall consensus/high concordance on the grossing and reporting of the pancreatic neck, uncinate/SMA margin, and resected portal vein/SMV while grossing in relationship to the posterior and anterior surfaces reached consensus/high concordance only in the Americas.

Opinions differed among pathologists about the statement that perpendicular sectioning of uncinate/SMA margin and posterior surface led to an overestimation of total lymph node count (PS12, Table 2). About half of the Asian (50.0%) and European (54.0%) pathologists disagreed, while pathologists from the Americas either agreed (40.0%) or were neutral (35.4%) to the statement. There was also discordance on whether the vascular groove/bed should be entirely submitted for evaluation and whether the tumor distance from the vascular groove/bed should be reported (PS13–14, SS12–13, Table 2). Only pathologists from Asia (87.5%) and surgeons from Europe (83.3%) reached consensus that the tumor distance from the vascular groove/bed should be reported (PS14, SS13, Table 2), and the surgeons from Europe and Asia reached consensus/high concordance (83.3% and 76.7%) that the entire vascular groove/bed should be submitted (SS12, Table 2). Therefore, there was considerable discordance on the impact of perpendicular sectioning on lymph node count and the vascular groove/bed grossing and reporting.

R1 versus R0 Issue

The pathologists had high concordance (76.5%) with the statement “ink on tumor (tumor cells extends to ink) is equivalent to R1 only in areas designated as margin, not surface” (PS18, SS16, Table 2). However, no consensus was reached when the statements regarding R1 status included tumor equal to or within 1 mm (74.3% for PS17; 71.3% pathologists and 60.3% surgeons for PS20, SS18, Table 2). When the overarching statements were assessed

by geographic regions, for the statement “tumor distance from the inked margin equal to 1 mm is still positive” (PS17, Table 2), European pathologists were in consensus (81.0%). In contrast, 70.8% and 50.0% of pathologists from the Americas and Asia agreed, respectively. That said, the Asian pathologists were in consensus (87.5%) when specifically asked if tumor cells extend to ink is equivalent to R1 only in areas designated as margin (PS18, Table 2).

The survey also highlighted how the assessment of surfaces remains controversial, particularly in categorizing R1 versus R0. No consensus was reached by pathologists (60.3% disagreed) and surgeons (54.8% disagreed) for the statement tumor on the inked area designated as surface should be considered R1 (PS19, SS17, Table 2). This interpretation remained true when analyzed by geographic regions (61.5% of pathologists and 66.7% of surgeons from the Americas, 50.0% of pathologists and 48.8% of surgeons from Asia, and 60.3% of pathologists and 50.0% of surgeons from Europe disagreed with the statement). Along the same lines and as expected, there was a greater discordance (70.6% for pathologists and 71.2% for surgeons) when the statement included “tumor within 1 mm of surface“ (PS21 and SS19, Table 2). When analyzing the interpretation per geographic regions, Asian pathologists (87.5%) and American pathologists (75.4%) and surgeons (75.0%) reached consensus/high concordance in disagreeing with that statement, when compared to the other participants (63.5% pathologists and 50.0% surgeons in Europe, and 72.1% surgeons in Asia).

Interpretations of pT4 Category

There was no consensus by pathologists (52.9%) and surgeons (49.3%) with the statement “invasion of tumor into portal vein/SMV invasion (even when resected) should be staged as pT4” (PS23, SS21, Table 2). Interestingly, while most surgeons from the Americas and Europe (66.7% for both) agreed with designating portal vein/SMV invasion as pT4, 51.2% of the Asian surgeons disagreed with this approach. Similarly, when asked about pT4 categorization for invasion into other organs (stomach, spleen, adrenal, kidney, etc.), even when resected (PS24, SS22, Table 2), most pathologists (73.5%) and surgeons (74.0%) agreed with that position. However, no consensus was reached except European pathologists (82.5%) and surgeons from the Americas and Europe (83.3% for both). Lastly, pathologists (80.9%) and surgeons (87.7%) were in consensus that when a separately submitted tissue labeled as “celiac axis” has carcinoma confirmed by a pathologist, it should be staged as pT4 (PS25, SS23, Table 2).

DISCUSSION

Many topics pertinent to grossing pancreatoduodenectomy specimens and their reporting have sparked debate over the years among pathologists and surgeons worldwide. Regional preferences regarding specific grossing techniques and nomenclature are also well-known in the pathology community. The goal of the survey was to gain insight into perspectives and potential alignment among pathologists and surgeons on various aspects of grossing, reporting, and staging PDAC.

While our survey results showed there was consensus the uncinate process (regardless of the terminology used) is a margin, there was no consensus whether other surfaces including vascular groove, posterior surface, and anterior surface, should be designated as margins. However, there was consensus among all participants that all surfaces should be reported, whether they are considered margins. CAP and AJCC guidelines also consider uncinate process as a margin and accept other terminologies such as SMA and retroperitoneal. The literature has introduced confusion due to differing geographic regional opinions and alternating use of the terms surface or margin for the same anatomic regions over time. Verbeke et al. advocated for all pancreatic surfaces (including anterior, posterior, and SMV groove) as margins, and over the years introduced various terminology for margins ("posterior" for uncinate margin as well as the posterior surface in 2006; "medial" for the vascular groove in 2008, and SMA for uncinate margin in 2013), possibly reflecting the evolution of the understanding of various grossing techniques[8, 24, 28]. Other European oncology groups (Westgard and Khalifa) also took a similar approach, which considered all the surfaces as margins[15, 16]. In 2010, Jamieson (European surgeon) introduced the concept of *mobilization* (including posterior and anterior surfaces) margins versus the *transected* (including pancreatic resection margin, uncinate margin, and vascular groove) margins, depending on whether they were dissected or transected.[22] In 2012 and 2013 studies by Gnerlich[18] (from USA) and Maksymov[11] (from Canada) did not include the anterior surface in the margins assessment. In 2017, a study from Japan included all surfaces as margins[23].

To summarize, all these studies have defined margins differently. Furthermore, CAP and AJCC do not acknowledge vascular groove as a margin, explaining why most pathologists from America do not consider the vascular groove as a margin. On the other hand, most Asian and European pathologists consider the vascular groove a margin because their literature about pancreatic margins has included vascular groove as a margin[8, 13, 22–26, 28, 29, 40, 41]. SMV is often surgically isolated from the pancreas at the vascular groove. However, unlike the uncinate margin, most of the time, it tends to come off readily without dissection unless the tumor invades into the SMV or there is associated inflammation and/or fibrosis. Therefore, technically it could be regarded as a "mobilization" margin or a surface. For this reason, other studies have not included vascular groove as a margin[4, 15, 17].

Similarly, there is no consensus about the posterior surface, although 65% of European pathologists consider the posterior surface as a margin. The posterior surface generally comes off readily but may need minimal dissection. Since it comes off readily, CAP and some investigators consider the posterior surface as a surface and not a margin[4, 15, 17, 20, 42]. On the other hand, since some dissection may be involved, it is considered as a margin in some studies[11, 13, 14, 16, 18, 23, 25, 26, 29, 40, 41] and accordingly, a significant number of participants consider posterior surface as a margin. Despite this debate of whether the posterior surface represents a margin or not, the posterior surface involvement may have a higher chance of local recurrence as it has access to the retroperitoneum. However, the posterior surface by itself (excluding uncinate) has not been studied previously.

Our results did not find consensus amongst pathologists and surgeons whether the anterior surface should be regarded the same as the posterior surface even though both surfaces are

generally smooth. Interestingly, although most pathologists and surgeons who participated in our survey disagreed that the anterior surface should be reported as a margin, there is an opposite opinion between European pathologists and surgeons. Most European surgeons (83.3%) agreed that the anterior surface should be reported as a margin, while less than half of the European pathologists agreed (41.3%). This finding highlighted a need for greater communication between the pathologists and surgeons on this issue in Europe. The anterior surface is more often peritonealized than the posterior surface, which may be why the anterior surface in many studies was excluded as a margin[4, 11, 15–18, 25, 29, 42]. Verbeke et al., however, regarded anterior surface as a margin in multiple papers (one study followed by multiple review papers), and so did Nitta and colleagues[8, 13, 14, 23, 24, 28, 32]. Furthermore, when our survey specifically asked whether this should be interpreted as R1, most surgeons and pathologists appeared resistant to this idea. Regardless of whether the anterior surface is a margin or not, there is consensus among pathologists and surgeons that the involvement of the anterior surface by tumor should be reported, which may be associated with a potential higher chance of peritoneal recurrence, though not proven.

There are debates on how to standardize the pancreatoduodenectomy grossing protocol and which protocol provides the most accurate and relevant prognostic information. Two grossing protocols are most commonly used, bivalve and axial sectioning protocols.[4, 7, 13, 14, 43] There is also a third less commonly used bread loaf slicing method that the pancreas is serially sectioned perpendicular to the longitudinal axis of the pancreatic neck.[14] The bivalve protocol sections along the main pancreatic duct and common bile duct plane after probing both ducts; this technique permits visualization of intraductal lesions such as intraductal papillary mucinous neoplasm (IPMN) as well as subclassify and stage ampullary tumors.[4] The axial protocol serially sections the pancreas perpendicular to the longitudinal axis of the descending duodenum; with this approach, the size of a tumor can be easily assessed, particularly in neoadjuvant-treated tumors. Because both methods have advantages and disadvantages, either approach is suitable provided pertinent findings are properly documented.

The survey results are not entirely surprising because it reflects a wide range of different practices and opinions about how pancreatoduodenectomy specimens should be handled and reported. Overall, within these limitations, there appears to be a consensus regarding how the pancreatic neck margin and uncinate/SMA margin should be sectioned, submitted, and reported. Specifically, the pancreatic neck margin should be entirely submitted en face and, if the tumor is present, qualifies it as R1. This consensus is expected since this approach is adopted by most, if not all, institutions currently. Because neck margin is often submitted for frozen section in some institutions, the en-face approach becomes the practical solution to examining this margin. Unfortunately, this approach conflicts with the “1 mm” criteria that are advocated in various guidelines. There is a broad consensus that the uncinate/SMA margin should be sectioned perpendicularly and entirely submitted, and the tumor distance from the margin should be reported, which is optional in the new version of the CAP Cancer Protocol (v4.1.0.0). Entirely submitting the uncinate/SMA margin is also recommended by many experts in the field regardless of grossing method.[4, 14] Regardless of the controversies, there are studies, which found that the extent of tissue sampling has a direct impact on the accuracy of the margin assessment.[24, 28] A study also found R1 resection to have significant

impact on long-term patient outcome using standardized pathologic evaluation and most R1 margins are the uncinate margin.[41] Whether representative sections of the posterior and anterior surfaces/margins are adequate has consensus/high concordance in the Americas, but not in Europe and Asia. The differences in approaches may also be partly attributable to healthcare practices. For example, in the United States, it would prove highly challenging to advocate total sampling of a pancreatoduodenectomy specimen, especially for a tumor like PDAC. The pathology report contents merely impact survival differences by weeks or a few months. While academicians who are interested in this topic strive to be as thorough as possible, this may prove challenging to adopt in the daily practices of community pathology settings given the cost-containment era. In contrast, in some countries like Japan, where complete sampling of cancers is quite common for any organ, complete sampling of PDAC is easy to adapt. Given that axial sectioning protocol is favored in Europe and Asia,[7, 44] it is understandable that pathologists and surgeons from Europe and Asia disagreed that representative sections of the posterior and anterior surfaces are adequate for evaluation.

Diverse opinions exist whether perpendicular sectioning of uncinate/SMA and posterior surface/margin leads to inaccurate or an overestimation of total lymph node count. A recent comparison study of all three grossing protocols showed that the bivalve protocol yielded more lymph node count and lymph node metastasis than the other two grossing protocols, supporting that different grossing protocols can affect lymph node yield.[45] However, both axial and bivalve protocols require perpendicular sectioning of uncinate/SMA and posterior surface/margins. Therefore, this controversial result does not necessarily support one or the other grossing protocol. Another statement that failed to reach consensus is whether the vascular groove/bed should be entirely submitted and tumor distance reported. Representative perpendicular sections from the closest tumor to the vascular bed are usually considered adequate according to the bivalve protocol, but this is often not the case according to the axial protocol.[4, 14] The argument that random sections of the vascular bed are adequate to document the closest tumor stems from the fact that this area has compact pancreatic tissue, and carcinoma extending to this focus is typically grossly visible. In contrast, the uncinate margin is rich in adipose tissue and often harbors grossly undetectable carcinoma, and therefore this area needs more extensive sampling to detect microscopic disease.[46, 47]

What represents a positive margin (R1) has been a source of debate among surgeons and pathologists. More recently published studies have drawn attention to this topic due to the higher rates of R1 reporting associated with newer grossing techniques.[22, 24–26, 48] The increased rates of R1 resections were likely a reflection of a more thorough pathologic evaluation and not necessarily attributed to changes in surgical techniques. The significance of an R1 resection remains poorly understood because in some studies it lacks correlation with survival data.[13, 15, 17, 22, 24, 26, 48–53] Furthermore, it is understandable that R1 rates varied widely among studies, ranging from 16%−80%[13, 26] if one considers all possible factors that play a role in the analysis including differences in grossing technique, sampling, geographic (regional) definitions of R1, and neoadjuvant therapies. Adsay et al. discovered microscopic foci of carcinoma in shaved sections of peripancreatic soft tissues. They proposed this may explain why the vast majority of PDAC ultimately progress locally, regardless of whether the shave is taken from a surface or the margin.[46, 47]

Traditionally, tumor on ink at a margin (tumor cells seen in direct contact with ink) on histologic slides has been considered by pathologists a positive margin (R1). However, multiple studies showed that the tumor recurrence rates are similar between tumor at the margin and within 1 mm of the margin.[25, 31, 54] European countries adopted the expanded definition of R1 to include cases with tumor cells within 1 mm from an inked margin as part of the R1 spectrum[22, 55] similar to the approach in rectal carcinoma. CAP and AJCC subsequently acknowledged the “1 mm rule” in recent guidelines for reporting exocrine pancreas resection margin. Since then, there has been a debate regarding the feasibility of applying such criteria to the uncinate margin alone or all margins in a pancreatoduodenectomy specimen. Confusion remains at some level when dealing with surfaces, including anterior surface. Although our survey results did not show consensus about R1 definition statements, most pathologists (74.2% for PS17 to 71.3% for PS20) and surgeons (54.7% for SS18) agreed that tumor at or within 1 mm from a margin, not surface, should be considered R1, while they opposed this definition when dealing with a surface. In summary, our results suggest that although most participants (82.2% for PS8, SS8) were in favor of reporting tumor at a surface, it appeared that most (70.8% for PS21, SS19) were against categorizing tumor within 1 mm of the surface as an R1 resection.

According to the AJCC 8th edition manual, the definition of pT4 is based on unresectable status (defined clinically-radiologically) or by histologic involvement of the celiac axis, superior mesenteric artery, or common hepatic artery. According to current recommendations, local extension of the tumor beyond the pancreas and into adjacent tissues (including portal vein) does not impact T staging. In keeping with the recommendations, there was consensus on designating pT4 when tissue separately submitted as “celiac axis” was histologically positive. This fact could be surprising for those in the clinical community that equates pT4 tumors to the concept of “unresectable” tumors.

A standardized grossing and reporting of the pancreatoduodenectomy specimen is crucial for precise determination of tumor origin, staging, treatment response, post-operative therapies, and uniform prognostication.[6] As better early diagnostic biomarkers and new effective therapies emerge, the uniform assessment and reporting of pancreatoduodenectomy specimens will become even more important than they may be today. The distinction between surface and margin may impact patients’ and surgeons’ view of the success of their surgeries and, potentially have implications on the use of postoperative radiation therapy and adjuvant chemotherapy regimen. According to the American Society of Clinical Oncology clinical practice guidelines, adjuvant chemoradiation therapy may be offered to patients who did not receive neoadjuvant therapy with R1 resection and/or have positive lymph node after completion of 4–6 months of systemic adjuvant chemotherapy.[56, 57] Therefore, standard margin and lymph node assessments are critical for post-operative patient management. Further studies on controversial issues regarding grossing and reporting pancreatoduodenectomy specimens revealed by this study using standardized protocols are needed to address these questions. We hope that this study will serve as the first step towards the goal of standardization.

We acknowledge several limitations in our study, including 1) results presented restricted to those whom we had an email address and were dependent on participation during the

survey timeframe; 2) practice setting of the survey participants' are unknown, but we suspect an academic bias; 3) there was no opportunity for clarifications or discussion about the survey statements; 4) despite many statements having illustrated figures, misinterpretation is possible; and 5) geographic (regional) preferences for specific practice realities, grossing techniques, reporting and diagnostic interpretation exist.

In summary, the group did not attempt to develop a consensus guideline for handling pancreatoduodenectomy specimens but did reveal existing perspectives among pathologists and surgeons. Based on these survey results, the following statements had consensus/high concordance by pathologists and surgeons, except for statement 6 surgeons reached no concordance:

1. The term margin applies only to the portion of the specimen dissected by the surgeon.
2. The term surface refers to tissue that comes off readily without dissection.
3. The uncinate margin is accepted as a margin.
4. The pancreatic neck margin should be entirely submitted en face, and if tumor on the slide, then is equivalent to R1.
5. The uncinate/SMA margin should be submitted entirely and perpendicularly, and tumor distance from the uncinate/SMA margin should be reported.
6. Ink on tumor or at or within 1 mm to the tumor is considered equivalent to R1 only in areas designated as margin, not surface.
7. Carcinoma involving separately submitted celiac axis in a pancreatoduodenectomy should be staged as pT4.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The authors thank Vincent Hoang, UCSF Department of Pathology, for posting the survey and collating the survey data. We appreciate the tremendous support from the Pancreatobiliary Pathology Society, Digestive Disease Working Group of the European Society of Pathology (ESP) (Dr. Jean-François Fléjou), Gastrointestinal Pathology Working Group of the Spanish Society of Pathology (SEAP) (Dr. Miriam Cuatrecasas), Dr. Manuel Rodriquez-Justo from the United Kingdom, Hepato-Pancreato-Biliary Working Groups of Federation of Turkish Pathologic Societies, The Americas Hepato-Pancreato-Biliary Association (AHPBA), Korean Association of Hepatobiliary Pancreatic Surgery, and Japanese Society of Hepato-Biliary-Pancreatic Surgery who disseminated the survey to their members. Jiaqi Shi was supported in part by the National Cancer Institute of the National Institutes of Health under award number K08CA234222.

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TABLE 1.

Number of Survey Statements that Achieved Consensus

Geographic region(s)	Pathologists N (%)	Surgeons N (%)
All three*	7/25 (28.0%)	7/23 (30.4%)
Americas	10/25 (40.0%)	8/23 (34.8%)
Asia	10/25 (40.0%)	10/23 (43.5%)
Europe	10/25 (40.0%)	16/23 (69.6%)

*Americas, Asia and Europe

TABLE 2.

Summarized Analyses of Responses to Each Statement

Statement	Participants' specialty and response	Participants that agreed or disagreed N (%)	Overall consensus or high concordance achieved*	Geographic regions with consensus (Geographic regions with high concordance)*
PS1/SS1.The term margin applies ONLY to the border cut (divided or dissected) by the surgeon to separate the tissue from other body parts (i.e. something that the surgeon has technical control of).	Pathologists agreed	121/136 (89.0)	Consensus	Americas and Asia (Europe)
	Surgeons agreed	58/73 (79.5)	High concordance	Asia (Americas)
PS2/SS2. The term surface refers to tisue that comes off readily/smoothly reflects off (without the surgeon cutting it – in other words, there is nothing the surgeon could have done to affect it	Pathologists agreed	126/136 (92.6)	Consensus	Americas and Europe (Asia)
	Surgeons agreed	63/73 (86.3)	Consensus	Americas and Asia
PS3/SS3. The area indicated by the white arrows or encircled by white dotted line represents the uncinate/SMA margin.	Pathologists agreed	126/136 (92.6)	Consensus	All three regions
	Surgeons agreed	66/73 (90.4)	Consensus	All three regions
PS4/SS4. The vascular groove/bed (outlined by yellow dotted line), corresponds to the indentation created by superior mesenteric/portal vein. This area should be reported as a margin even if it can be surgically teased apart and comes off readily and without adhesions (if ink on tumor, then equivalent to R1).	Pathologists agreed	89/136 (65.4)	None	Asia and Europe
	Surgeons agreed	54/73 (73.9)	None	Europe (Asia)
PS5/SS5. This side of the pancreas (posterior), 180 degrees opposite the anterior side, should be reported as a margin even if it is not dissected surgically, but comes off readily (if ink on tumor, then equivalent to R1).	Pathologists agreed	68/136 (50.0)	None	None
	Surgeons agreed	41/73 (56.2)	None	Europe
PS6/SS6. This side of the pancreas (anterior, bracketed in aqua) should be reported as a margin even if it is not dissected surgically, but comes off readily (if ink on tumor, then equivalent to R1).	Pathologists disagreed	87/136 (64.0)	None	Asia (Americas)
	Surgeons disagreed	31/73 (42.5)	None	Europe [+]
PS7/SS7. It is contradictory to regard the posterior side of the pancreas a margin, but NOT regard the anterior side of the pancreas a margin even though both are not surgically dissected and comes off readily.	Pathologists agreed	78/136 (57.4)	None	None
	Surgeons agreed	43/73 (58.9)	None	None (Americas)
PS8/SS8. Free surfaces involved by tumor should also be reported by the pathologist.	Pathologists agreed	107/136 (78.7)	High concordance	Asia and Europe
	Surgeons agreed	65/73 (89.0)	Consensus	All three regions
PS9/SS9. The pancreatic neck margin (outlined by black dotted line) should be evaluated by the pathologist and entirely submitted en face (if tumor on the slide, then equivalent to R1).	Pathologists agreed	120/136 (88.2)	Consensus	All three regions
	Surgeons agreed	68/73 (93.2)	Consensus	All three regions
PS10/SS10. The uncinate/SMA margin (area indicated by the white arrows/within dotted line) should be submitted entirely for microscopic evaluation by the pathologist.	Pathologists agreed	108/136 (79.4)	High concordance	Asia (Americas and Europe)
	Surgeons agreed	67/73 (91.8)	Consensus	All three regions
PS11/SS11. The tumor distance from the uncinate/SMA margin should be reported (perpendicular sections must be taken).	Pathologists agreed	113/136 (83.1)	Consensus	All three regions
	Surgeons agreed	55/73 (75.3)	High concordance	Americas and Europe
PS12. Perpendicular sectioning of uncinate/SMA and posterior surface/margin leads to inaccurate/overestimation of total lymph node count.	Pathologists disagreed	54/136 (39.7)	None	None
PS13/SS12. The vascular groove/bed (outlined by yellow dotted line), indentation created by superior mesenteric/	Pathologists agreed	57/136 (41.9)	None	None

Statement	Participants' specialty and response	Participants that agreed or disagreed N (%)	Overall consensus or high concordance achieved*	Geographic regions with consensus (Geographic regions with high concordance)*
portal vein, should be submitted entirely for microscopic evaluation by the pathologist.	Surgeons agreed	54/73 (74.0)	None	Europe (Asia)
PS14/SS13. The tumor distance from the vascular groove/bed should be reported (perpendicular section must be taken).	Pathologists agreed	83/136 (61.0)	None	Asia
	Surgeons agreed	50/73 (68.5)	None	Europe
PS15/SS14. Representative sections of the closest approach of grossly visible tumor to the posterior pancreatic surface/ margin are adequate for pathologic assessment.	Pathologists agreed	103/136 (75.7)	High concordance	Americas
	Surgeons agreed	47/73 (64.4)	None	None (Americas)
PS16/SS15. Representative sections of the closest approach of grossly visible tumor to the anterior pancreatic surface/ margin (aqua area bracketed) are adequate for pathologic assessment.	Pathologists agreed	107/136 (78.7)	High concordance	Americas
	Surgeons agreed	46/73 (63.0)	None	None (Americas)
PS17. Current CAP pancreas protocol and AJCC exocrine pancreas chapter cites tumor "at or within 1 mm of margin" constitutes a positive margin. Therefore tumor distance from the inked margin equal to 1 mm is still positive.	Pathologists agreed	101/136 (74.3)	None	Europe
PS18/SS16. Ink on tumor (tumor cells extends to ink) is equivalent to R1 only in areas designated as margin, not surface.	Pathologists agreed	104/136 (76.5)	High concordance	Asia
	Surgeons agreed	54/73 (74.0)	None	None (Americas)
PS19/SS17. Ink on tumor (tumor cells extends to ink) is equivalent to R1 even in areas designated as surface.	Pathologists disagreed	82/136 (60.3)	None	None
	Surgeons disagreed	40/73 (54.8)	None	None
PS20/SS18. Tumor distance within 1 mm to ink is equivalent to R1 only in areas designated as margin, not surface.	Pathologists agreed	97/136 (71.3)	None	None
	Surgeons agreed	44/73 (60.3)	None	None
PS21/SS19. Tumor distance within 1 mm to ink is equivalent to R1 even in areas designated as surface.	Pathologists disagreed	96/136 (70.6)	None	Asia
	Surgeons disagreed	52/73 (71.2)	None	None (Americas)
PS22/SS20. The resected segment of portal vein/SMV must be properly marked by the surgeon in order for it to be evaluated by a pathologist.	Pathologists agreed	111/136 (81.6)	Consensus	Americas and Europe (Asia)
	Surgeons agreed	64/73 (87.7)	Consensus	Asia and Europe (Americas)
PS23/SS21. Invasion of tumor into portal vein/SMV, even when resected, should be staged as pT4.	Pathologists agreed	72/136 (52.9)	None	None
	Surgeons agreed	36/73 (49.3)	None	None
PS24/SS22. Another organ (stomach, spleen, adrenal, kidney, etc.) involved by tumor, even when resected, should be staged as pT4.	Pathologists agreed	100/136 (73.5)	None	Europe
	Surgeons agreed	54/73 (74.0)	None	Americas and Europe
PS25/SS23. A pancreatectomy is performed and a separately submitted tissue labeled as "celiac axis" has carcinoma confirmed by a pathologist. This should be staged as pT4.	Pathologists agreed	110/136 (80.9)	Consensus	Americas (Asia and Europe)
	Surgeons agreed	64/73 (87.7)	Consensus	Americas and Asia

PS: pathologist's statement; SS: surgeon's statement;

*≥80% equates to consensus, and ≥75% but <80% equates to high concordance;

[+]>80% of European surgeons agreed (consensus).