

Interobserver variability in intraductal papillary mucinous neoplasm subtypes and application of their mucin immunoprofiles

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Intraductal papillary mucinous neoplasm is considered a precursor lesion to pancreatic adenocarcinoma. These are further classified into four histologic subtypes: gastric, intestinal, pancreatobiliary, and oncocytic. The first aim of this study was to assess the interobserver variability among five gastrointestinal pathologists in diagnosing intraductal papillary mucinous neoplasm subtypes by morphology alone. The second aim of the study was to compare intraductal papillary mucinous neoplasm subtypes, which received consensus diagnoses ($\geq 80\%$ agreement) with their respective mucin immunoprofiles (MUC1, MUC2, MUC5AC, MUC6, and CDX2). A consensus histologic subtype was reached in 58% of cases (29/50) among the five gastrointestinal pathologists. Overall there was moderate agreement ($\kappa = 0.41$, $P < 0.01$) in subtyping intraductal papillary mucinous neoplasms without the use of immunohistochemistry. The histologic subtype with the best interobserver agreement was intestinal type ($\kappa = 0.56$, $P < 0.01$) followed by pancreatobiliary, gastric, mixed, and oncocytic types ($\kappa = 0.43$, $P < 0.01$; $\kappa = 0.38$, $P < 0.01$; $\kappa = 0.17$, $P < 0.01$; $\kappa = 0.08$, $P < 0.04$, respectively). Both kappa values for mixed and oncocytic subtypes were likely artificially low due to the underrepresentation of these subtypes in this study and not a true indication of poor interobserver agreement. Following an intradepartmental consensus meeting between two gastrointestinal pathologists, 68% of cases (34/50) received a consensus intraductal papillary mucinous neoplasm subtype. Sixty-nine percent of cases (11/16) that did not receive a consensus intraductal papillary mucinous neoplasm subtype could be classified based on their respective immunoprofiles. Standardizing the use of immunohistochemistry with a mucin immunopanel (MUC1, MUC2, MUC5AC, and MUC6) may improve the agreement of diagnosing intraductal papillary mucinous neoplasm histologic subtypes.

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Intraductal papillary mucinous neoplasm (IPMN) was coined in 1994 and is defined as a preinvasive pancreatic neoplasm arising in pancreatic ducts that forms a grossly visible mass.¹ A consensus meeting in 2003 further classified IPMN into four histologic subtypes: gastric, intestinal, pancreatobiliary, and oncocytic based on morphology and immunohistochemistry.² MUC1, MUC2, and MUC5AC immunohistochemical stains were used in the initial classification. Additional studies observed MUC6 and CDX2 as useful gastric and intestinal markers in IPMNs, respectively.^{3,4}

Following categorization into histologic subtypes, multiple clinicopathological correlation studies were performed. Gastric subtype is commonly seen in branch duct IPMNs whereas intestinal and pancreatobiliary subtypes usually involve the main pancreatic duct. Gastric and pancreatobiliary subtypes are more often associated with invasive tubular adenocarcinoma *versus* intestinal subtype, which is frequently associated with invasive colloid carcinoma.^{5–8} Furthermore, studies have reported conflicting evidence on whether the histologic IPMN subtype has prognostic significance.^{8–12}

The Verona consensus meeting in 2013 recently led to the publication of guidelines for pathologic reporting of IPMN with the recommendation that pathologists provide a histologic subtype.¹³ Although most previous studies used morphology and immunohistochemistry to designate the IPMN subtype, this is not necessarily implemented as

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standard practice. Our study analyzes interobserver agreement between specialized gastrointestinal pathologists to subtype IPMN using morphology alone. In addition, we compare their consensus morphologic diagnoses with the immunohistochemical profiles for each case.

Materials and methods

Case Selection

The study included 50 cases of IPMN during 2000–2013 from the surgical pathology archives of the University of Chicago (27 cases) and Cleveland Clinic (23 cases). Histological slides of the cases were reviewed by pathologist (SX) or (XL) with one representative hematoxylin and eosin stained slide selected from each case. The criterion for the representative slide was that there would be substantial lesional tissue to make a histologic subtype diagnosis without discriminating between the presence of one or more subtypes.

Interobserver Agreement

Five pathologists with specialized training in gastrointestinal pathology were chosen to individually review the cases and subtype each IPMN as gastric, intestinal, pancreatobiliary, oncocytic, or mixed. Mixed subtype was designated as having more than one subtype, each comprising $\geq 25\%$ of the lesion. Additional parameters recorded were the grade of dysplasia (low, intermediate, or high) and the presence or absence of invasion. All the data received were generated based on hematoxylin and eosin stained slides without the use of special or immunohistochemical stains.

A consensus diagnosis for each category was defined as having four of five pathologists in agreement with one another, or $\geq 80\%$.

Cases that did not meet the 80% agreement for IPMN subtyping were revisited by two pathologists at an intradepartmental consensus meeting. The main reason of this consensus meeting was to render a 'final' histotype designation for subsequent immunophenotypic study, when possible.

IPMN subtypes were designated for each case when there was $\geq 80\%$ interobserver agreement following the intradepartmental consensus meeting. These cases were subsequently correlated with the immunohistochemical panel performed. The cases with $< 80\%$ interobserver agreement were categorized into IPMN subtypes using previously published immunohistochemical data on IPMN classification, when possible.^{2,4}

Immunohistochemical Studies

All 50 cases of IPMN had immunohistochemical staining performed on 5- μm tissue sections from the

same formalin-fixed, paraffin-embedded tissue block, which was selected for initial hematoxylin and eosin stained slide examination. MUC1 (MA695; NovoCastra, UK; 1:400), MUC2 (CCP58; NovoCastra; 1:25), MUC5AC (CLH2; NovoCastra; 1:25), MUC6 (CLH5; NovoCastra; 1:25), and CDX2 (CDX2-88; Biogenex, Fremont, CA, USA; 1:100) immunohistochemical staining was performed on all cases. The immunostains had appropriate controls and were reviewed by one pathologist (SX). The immunohistochemistry was quantitatively scored based on percent immunoreactivity in the lesional cells. A positive result was associated with $\geq 10\%$ positive staining and a negative result associated with $< 10\%$ positive staining.

Statistical Analysis

The interobserver agreements were calculated using Fleiss' kappa statistic (κ). A κ -value ranging from 0.00 to 0.20 is slight agreement, 0.21–0.40 is fair agreement, 0.41–0.60 is moderate agreement, 0.61–0.80 is substantial agreement, and 0.81–1.00 is almost perfect agreement.¹⁴

Results

Agreement of IPMN Histological Subtypes

The interobserver variability for IPMN subtypes is summarized in Table 1. There was moderate agreement ($\kappa = 0.41$, $P < 0.01$) among the five gastrointestinal pathologists, overall. Intestinal subtype had the best agreement ($\kappa = 0.56$, $P < 0.01$), while oncocytic subtype had the poorest agreement ($\kappa = 0.08$, $P < 0.04$). Figure 1 represents cases of IPMN subtypes that received a consensus subtype followed by cases that lacked a consensus subtype and were classified by pathologists as either one of two specific subtypes.

Agreement of Grade of Dysplasia and Invasion

Table 2 shows results of interobserver variability in determining the presence or absence of dysplasia

Table 1 Kappa-values for interobserver reproducibility of intra-ductal papillary mucinous neoplasm subtyping

	κ -Value (95% confidence interval)	P-value
<i>Subtypes</i>		
Gastric	0.38 (0.30–0.47)	< 0.00001
Intestinal	0.56 (0.47–0.64)	< 0.00001
Pancreatobiliary	0.43 (0.34–0.51)	< 0.00001
Oncocytic	0.08 (0–0.17)	< 0.04000
Mixed	0.17 (0.08–0.26)	< 0.00001
Overall κ -value	0.41 (0.35–0.46)	< 0.00001

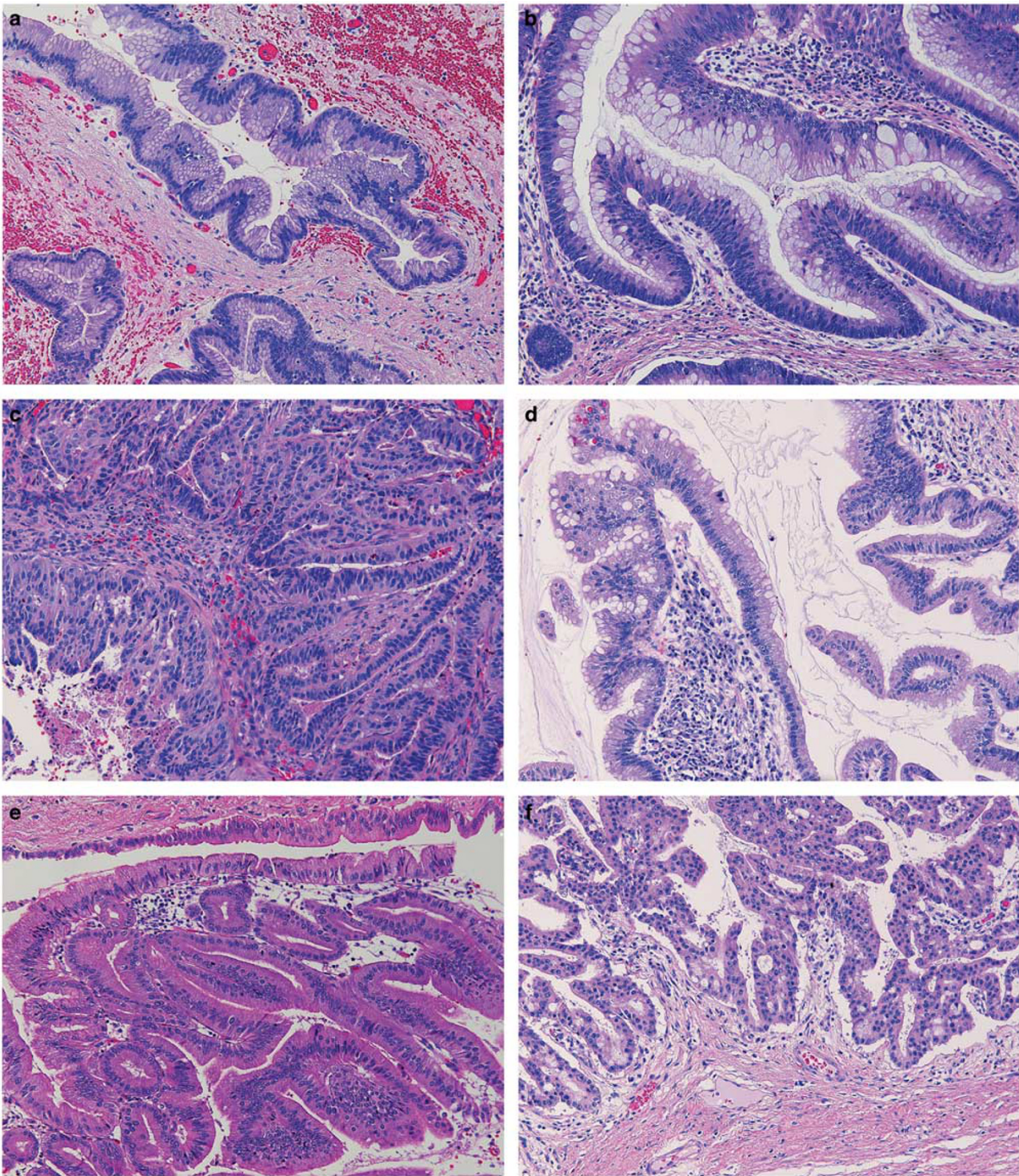


Figure 1 Representative hematoxylin and eosin stained slide images of the different morphologic subtypes of intraductal papillary mucinous neoplasm seen in our case series. Consensus diagnoses were achieved for gastric subtype (a), intestinal subtype (b), and pancreatobiliary subtype (c) in these cases. No consensus between gastric or intestinal subtype (d), no consensus between gastric or pancreatobiliary subtype (e), and no consensus for pancreatobiliary or oncocytic subtype (f) were achieved in these cases.

and invasion. Identifying low- and high-grade dysplasia had moderate agreement ($\kappa=0.45$, $P<0.01$ and $\kappa=0.60$, $P<0.01$, respectively) whereas intermediate dysplasia had slight agreement (0.18,

$P<0.01$). Overall, there was moderate ($\kappa=0.41$, $P<0.01$) and substantial ($\kappa=0.72$, $P<0.01$) agreement between the pathologists grading dysplasia and recognizing invasion, respectively.

Table 2 Kappa-values for interobserver reproducibility of grading dysplasia and identifying invasion in intraductal papillary mucinous neoplasm

	No. of cases classified with $\geq 80\%$ agreement (% of consensus cases)	κ -Value (95% confidence interval)	P-value
<i>Dysplasia</i>			
Low	11	0.45 (0.36–0.54)	< 0.00001
Intermediate	6	0.18 (0.10–0.27)	0.00002
High	14	0.60 (0.51–0.69)	< 0.00001
Overall κ -value		0.41 (0.35–0.47)	< 0.00001
Total no. of cases with $\geq 80\%$ agreement (% cases)	31 (62%)		
Presence or absence of invasion	46 (92%)	0.72 (0.63–0.81)	< 0.00001

Correlation Between Histological Subtyping and Grade of Dysplasia

Cases designated as having low-grade dysplasia consisted of 72.7% gastric, 0.0% intestinal, 0.0% pancreatobiliary subtypes, respectively and 27.2% without a consensus subtype. Intermediate grade dysplasia cases comprised 16.7% gastric, 16.7% intestinal, 0.0% pancreatobiliary, and 66.7% no consensus subtypes, respectively. Finally, high-grade cases were gastric, 14.3% intestinal, 21.4% pancreatobiliary, and 64.3% no consensus subtypes, respectively.

Recent Baltimore Consensus Meeting recommendations suggest collapsing the three-tiered system for grading dysplasia in pancreatic precursor lesions into two by combining low and intermediate grades and relabeling them all as low grade.¹⁵ After applying the two-tiered system, low-grade cases consisted of 56.7% gastric, 10.0% intestinal, 0.0% pancreatobiliary, and 33.3% no consensus subtypes, respectively, whereas high-grade dysplasia comprised 0.0% gastric, 14.3% intestinal, 21.4% pancreatobiliary, and 64.3% no consensus, subtypes, respectively.

Correlation Between Histological Subtyping and Immunohistochemistry

Table 3 summarizes the percent of cases that received a consensus diagnosis based on hematoxylin and eosin stained slides before and after an intradepartmental consensus meeting (58 and 68%, respectively). Thirty-four cases were classified as a specific subtype based on achieving a consensus diagnosis. The immunohistochemical profiles for these IPMN subtypes are shown in Table 4. MUC5AC followed by MUC6 were markers most commonly seen in gastric subtypes. MUC2 and CDX2 were mostly seen only in intestinal subtypes; however, MUC5AC was also seen in two-thirds of cases⁶ classified as intestinal subtype. Pancreatobiliary subtype did not have a consistent staining pattern, but was the only subtype with positive immunoreactivity for MUC1. In Figure 2, examples of IPMN

Table 3 Submitted intraductal papillary mucinous neoplasm subtypes by morphology

	No. of cases classified with $\geq 80\%$ agreement (% of consensus cases)	No. of cases following consensus meeting (%)
<i>Subtypes</i>		
Gastric	18	20
Intestinal	7	9
Pancreatobiliary	4	5
Oncocytic	0	0
Mixed	0 ^a	0 ^a
Total no. of cases with $\geq 80\%$ agreement (% cases)	29 (58%)	34 (68%)

^aAlthough cases were subtyped as mixed in certain cases, a consensus was not reached on which subtypes were present within the mix.

Table 4 Correlating intraductal papillary mucinous neoplasm histologic subtypes with immunohistochemistry

	MUC1	MUC2	MUC5AC	MUC6	CDX2
Gastric	0	1	20	13	0
Intestinal	0	9	6	0	8
Pancreatobiliary	3	1	3	1	1

subtypes and their respective immunoprofiles are presented.

Additionally, Figure 2 demonstrates a case without an assigned consensus IPMN subtype by morphology that can instead be classified based on immunohistochemistry. Overall, 11 of the 16 cases without a consensus subtype had a specific immunoprofile as seen in Table 5. Of the 11 cases, seven and four stained like gastric (MUC1–, MUC2–, MUC5AC+, MUC6+, and CDX2–) and intestinal (MUC1–, MUC2+, MUC5AC±, MUC6–, and CDX2±) subtypes, respectively. The remaining

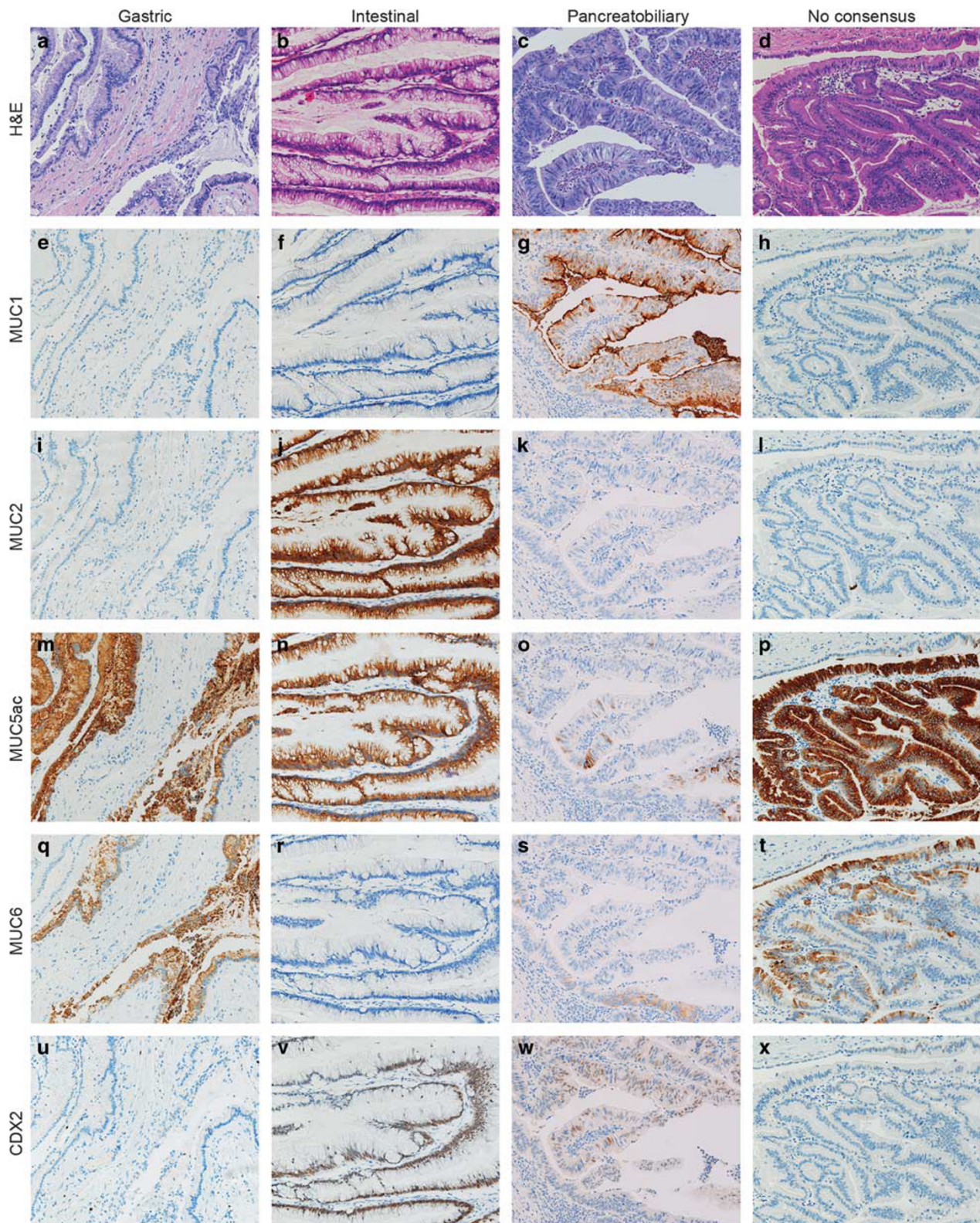


Figure 2 Hematoxylin and eosin stained slide images of the different morphologic subtypes of intraductal papillary mucinous neoplasm with corresponding immunohistochemical images. Representative images of cases with a consensus diagnosis of gastric subtype (a), intestinal subtype (b), and pancreatobiliary subtype (c). No consensus between gastric or pancreatobiliary subtypes was reached in this case (d). MUC5ac and MUC6 were positive (m, q), while MUC1, MUC2, and CDX2 were negative (e, i, u) in this case with gastric subtype. MUC2, MUC5ac, and CDX2 were positive (j, n, v), while MUC1 and MUC6 were negative (f, r) in this case with intestinal subtype. MUC1 and CDX2 were positive (g, w), while MUC2, MUC5ac, and MUC6 were negative (k, o, s) in this case with pancreatobiliary subtype. The case without a consensus diagnosis was MUC5ac and MUC6 positive (p, t), while MUC1, MUC2, and CDX2 negative (h, l, x).

Table 5 Correlating cases with no consensus on histologic subtypes with immunohistochemistry

Case #	MUC1	MUC2	MUC5AC	MUC6	CDX2	Subtype following immunohistochemistry
3	-	-	-	-	-	Inconclusive
8	-	-	+	+	-	Gastric
12	-	-	+	-	-	Inconclusive
20	-	+	+	+	+	Mixed
23	-	+	+	-	+	Intestinal
27	-	-	+	+	-	Gastric
28	-	+	+	-	-	Intestinal
29	-	-	+	+	-	Gastric
30	-	-	+	+	+	Mixed
32	-	+	-	-	+	Intestinal
33	-	-	+	-	-	Inconclusive
34	-	+	+	-	+	Intestinal
36	-	-	+	+	-	Gastric
38	-	-	+	+	-	Gastric
40	-	-	+	+	-	Gastric
48	-	-	+	+	-	Gastric

five cases had either no staining, (1) MUC5AC+ only (2) or immunoprofiles supportive of mixed subtypes (2).

Discussion

In this study, we show moderate agreement ($\kappa=0.41$, $P<0.01$) among five gastrointestinal pathologists in classifying IPMN subtypes using morphology alone with 58% of cases (29/50) receiving a consensus IPMN subtype. Additionally, 69% of IPMN cases without a consensus subtype (11/16) could be classified based on their immunoprofiles. A previous interobserver study grading Barrett's dysplasia among gastrointestinal pathologists by Downs-Kelly *et al*¹⁶ demonstrated fair overall agreement ($\kappa=0.30$), while another study by Kaye *et al*¹⁷ had improved overall interobserver agreement in grading Barrett's dysplasia following the use of p53 immunohistochemistry ($\kappa=0.42$ to $\kappa=0.48$ after the use of immunohistochemistry). These studies illustrate that moderate agreement in interobserver studies is not necessarily easy to achieve and that judicious use of immunohistochemistry can help with interobserver agreement.

As the largest interobserver study of IPMN in the literature, comprising five pathologists specialized in gastrointestinal pathology, this study demonstrates the difficulty of subtyping IPMN and the ability of immunohistochemistry to help subtype in cases with ambiguous morphology. Currently in our daily practice, we traditionally rely on morphology alone to determine the IPMN subtype in our resection specimens. However, most published clinicopathological correlation studies on IPMN use a combined method of morphology and immunohistochemistry to histologically subtype IPMN. Thus, in accordance to the recent guidelines that recommend pathologists provide a histologic subtype when reporting IPMN,

we suggest the use of immunohistochemistry in cases when a definitive subtype cannot be assigned with morphology alone.

A recent publication by Schaberg *et al*¹⁸ reported limited value in the use of immunohistochemistry in subtyping IPMN using the WHO classification for IPMN immunophenotypes. In their study immunohistochemistry was only performed on equivocal cases and only two of their nine ambiguous cases were further classified using immunohistochemistry. In the current study there are cases where a consensus diagnosis of an IPMN subtype was achieved using morphology on hematoxylin and eosin stained slides alone with corresponding immunohistochemistry demonstrating an overlap of mucin markers or the lack of specific MUC immunohistochemical staining. Our findings correlated with previous studies where MUC2 and CDX2 were seen in non-intestinal subtypes and most but not all intestinal subtypes had immunoreactivity with CDX2.^{3,4} When CDX2 was classified as positive (defined as $\geq 10\%$ immunoreactivity) in the intestinal subtypes though, all cases showed that $\geq 50\%$ of the lesional cells were positive. In addition, a lack of staining may also be seen in areas with high-grade dysplasia. Recognizing the limitations of immunohistochemistry, we recommend using it in conjunction with morphology, deferring to morphology to aid in differentiating discrepant immunohistochemical staining from the presence of more than one subtype.

Our study confirms the utility of MUC stains, especially MUC2 in identifying IPMN as intestinal subtype. In addition, MUC6 positivity in our study differentiates gastric from intestinal and pancreatobiliary subtypes, which can also be positive for MUC5AC. Similar to Basturk *et al*, MUC6 is positive in flat or cystic spaces with pyloric-like histology seen in our cases identified as gastric subtype. In cases identified as pancreatobiliary subtype however, only one of our cases had immunoreactivity with MUC6, unlike their study, which had weak but consistent expression of MUC6 in their pancreatobiliary IPMNs. This however may reflect our low number of pancreatobiliary cases.¹⁹ Previous studies have distinguished MUC1 as an aggressive marker in pancreatic neoplasms, positive in areas of invasive carcinoma and IPMN with high-grade dysplasia.²⁰⁻²² Though limited in the number of cases, the pancreatobiliary subtypes of IPMN in our study were the only ones with positivity for MUC1. We propose the ideal immunopanel in classifying IPMN subtypes to consist of MUC1, MUC2, MUC5AC, and MUC6.

Overall, sample size and unequal representation of all the subtypes were limitations in this study. This limitation is demonstrated by the poor interobserver agreement seen in the mixed and oncocytic subtypes, which we would expect to have better agreement in the setting of more cases. A study by Reid *et al*²³ demonstrated the ability to accurately provide a cytopathologic diagnosis of intraductal oncocytic papillary neoplasms using helpful cytomorphologic

features and Basturk *et al*²⁴ demonstrated distinct molecular characteristics in this subtype. This is significant given evidence that the oncocytic subtype carries a favorable long-term prognosis.^{25,26} Nevertheless, the cases in our study were representative of the IPMN specimens received at both institutions. Previous studies also demonstrate the greater prevalence of gastric and intestinal IPMN subtypes.^{7,8,27} The mixed subtype may have been difficult to assess due to the limited examination of the specimen by all the gastrointestinal pathologists, which is reflected in the poor interobserver agreement for this subtype. Nonetheless, the entirety of each case was seen by a gastrointestinal pathologist at his or her respective institution and the selected slide from each case should be considered representative of the overall lesion.

Although the clinicopathological significance of subtyping IPMN in a resection specimen is equivocal, the importance of identifying an invasive component for prognosis is undisputed. There was substantial agreement ($\kappa=0.72$, $P<0.001$) in this study for diagnosing invasion. While this received the highest κ -value, there was not complete concordance among the pathologists in all the cases. Hence, comprehensive sampling of the specimen is essential to ensure invasion is not missed since the associated presence of invasive adenocarcinoma affects patient prognosis and management.

Interestingly, classification of IPMN subtypes has been attempted preoperatively through immunohistochemical studies of pancreatic juice cytology by Hara *et al*.²⁸ Histological IPMN subtype diagnosed with pancreatic juice cytology was compared with the subtype diagnosis made at resection. With the use of MUC1, MUC2, and MUC5AC immunostains, the histological IPMN subtype was correctly diagnosed in 89% of cases (32/36) with a sensitivity and specificity of 86 and 100%, respectively. In order to stratify high- and low-risk patients with IPMN, Maker *et al*²⁹ and Yokoyama *et al*³⁰ looked at various mucin expression profiles in pancreatic cyst fluid and pancreatic juice through enzyme immunoassay and DNA methylation analysis, respectively. These studies use mucin expression profiles to help identify IPMN subtypes and highlight a potential use of IPMN subtyping in helping guide the surgeon when determining surgical management.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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