TABLE 1. Comparison of Pathologic Features Between IPNB-M and IPNB-NM, and Comparable Data on IPMN-P Derived From the Literature

	IPNB			
	IPNB-NM (n = 17)	IPNB-M (n = 10)	*P*	IPMN-P*
Size (average; cm)	2.7	3.4	0.60	3.7-4.3
Gross appearance				
Polypoid	9 (53%)	7 (70%)	0.08	Not classified
Polypoid-granular	6 (35%)	0 (0%)		
Granular	2 (12%)	3 (30%)		
Histopathologic type				
Gastric	1 (6%)	1 (10%)	0.003	31%
Intestinal	3 (18%)	8 (80%)		35%
Pancreatobiliary	13 (76%)	1 (10%)		22%
Maximum degree of cytoarchitectural atypia				
Adenoma or borderline	1 (6%)	1 (10%)	> 0.99	24%-38%
Carcinoma	16 (94%)	9 (90%)		62%-76%
Well: moderately: poorly differentiated	13: 3: 0	9: 0: 0	0.28	
Existence of various degrees of cytoarchitectural atypia	3 (18%)	8 (80%)	0.003	Usually
Depth of invasion				
Within ductal wall	8 (47%)	9 (90%)	0.04	55%-73%
Beyond ductal wall	9 (53%)	1 (10%)		27%-45%
Invasive pattern†				
Pushing growth margin	2 (22%)	1 (100%)	0.30	Not assessed
Infiltrating growth margin	7 (78%)	0 (0%)		
Existence of lymphovascular invasion	6 (35%)	0 (0%)	0.06	47% of invasive cases
Ki-67 labeling index‡	32 ± 15%	27 ± 11%	0.40	24%-40%
Existence of superficial spread	9 (53%)	3 (30%)	0.42	Often
Existence of multiple lesions	3 (18%)	1 (10%)	> 0.99	Sometimes
Existence of lymph node metastasis	2 (12%)	0 (0%)	0.52	0%-20%

*Data derived from the literature.[1,7,10,16,18–20,24]
†Data obtained from cases with invasive carcinoma.
‡Mean ± standard deviation.

abdominal pain and fever related to cholangitis or jaundice were the most common complaints among patients with and without mucin. Eight of 17 IPNB-NM (47%) were located in the intrahepatic bile duct, whereas 5 of 10 IPNB-M (50%) were located in the intrahepatic bile duct. A total of 9 patients with IPNB (33%) had histories of bile duct stones or bile duct stones detected perioperatively; 1 patient with IPNB-NM had common bile duct stones and 3 patients had intrahepatic bile duct stones, detected perioperatively, and 1 had a history of common bile duct stones. In patients with IPNB-M, 2 had histories of common bile duct stones, 1 had a history of common and intrahepatic bile duct stones, and 1 had intrahepatic bile duct stones detected perioperatively. One patient with IPNB-NM was diagnosed with sclerosing cholangitis during the diagnostic workup. Although a positive level (> 40 U/mL) of serum CA19-9 was more commonly observed in patients with IPNB-NM (11 cases) than in patients with IPNB-M (3 cases), this was not statistically significant ($P = 0.12$).

Eight patients with IPNB-NM underwent surgery more than hemihepatectomy with extrahepatic bile duct resection (BDR), 1 underwent hemihepatectomy with pancreatoduodenectomy, 1 hemihepatectomy, 2 hepatic segmentectomy with BDR, 2 hepatic segmentectomy, 1 BDR alone, and 2 pancreatoduodenectomy. Six patients with IPNB-M underwent surgery more than hemihepatectomy with BDR, 2 underwent hemihepatectomy, 1 hepatic caudate lobectomy with BDR, and 1 hilar BDR. Pathologic features are summarized in Tables 1 and 2.

Macroscopic Findings

In IPNB-NM, the average tumor size was 2.7 cm (range, 1.3 to 4.6 cm), whereas in IPNB-M, the average size was 3.4 cm (range, 1.5 to 5.0 cm). In 15 of 17 IPNB-NM, the tumors appeared as polypoid masses elevating into the lumen of the bile duct (polypoid type) (Fig. 1A). Among these tumors, 6 had clinically visible granular or small papillary mucosa in which the maximum height of mucosal protrusion was < 5 mm in the vicinity of the main polypoid mass (polypoid-granular type) (Fig. 1B). The other 2 IPNB-NM were composed of only granular mucosa (granular type) (Fig. 1C). Similarly, 7 IPNB-M were classified as polypoid type and 3 as granular type, in all of which intraductal mucin accumulation was noted.

Microscopic Findings

All neoplasms included a portion of papillary fronds with fine vascular cores. Coexistence of tubulopapillary growth was exhibited more commonly in IPNB-NM (12 cases) than in IPNB-M (2 cases).

On the basis of dominant morphologic features, 1 IPNB-NM was classified as the gastric type (Fig. 2A), 3 as

TABLE 2. Immunohistochemical Mucin Expression and p53 Nuclear Accumulation in IPNB-M and IPNB-NM and Nonpapillary Cholangiocarcinoma, and Comparable Data on IPMN-P Derived From the Literature

Tumor Type	MUC1	MUC2	MUC5AC	HGM	MUC6	p53
IPNB-M (n = 8)	3 (38%)	7 (88%)	7 (88%)	7 (88%)	1 (13%)	0 (0%)
IPNB-NM (n = 16)	13 (81%)	4 (25%)	12 (75%)	10 (63%)	9 (56%)	8 (50%)
Nonpapillary cholangiocarcinoma (n = 10)	10 (100%)	1 (10%)	7 (70%)	9 (90%)	3 (30%)	7 (70%)
IPMN-P*	11%-39%	42%-92%	97%-100%	NA	29%	0%

*Data derived from the literature.[4,8,14,16,24]
NA indicates not assessed.

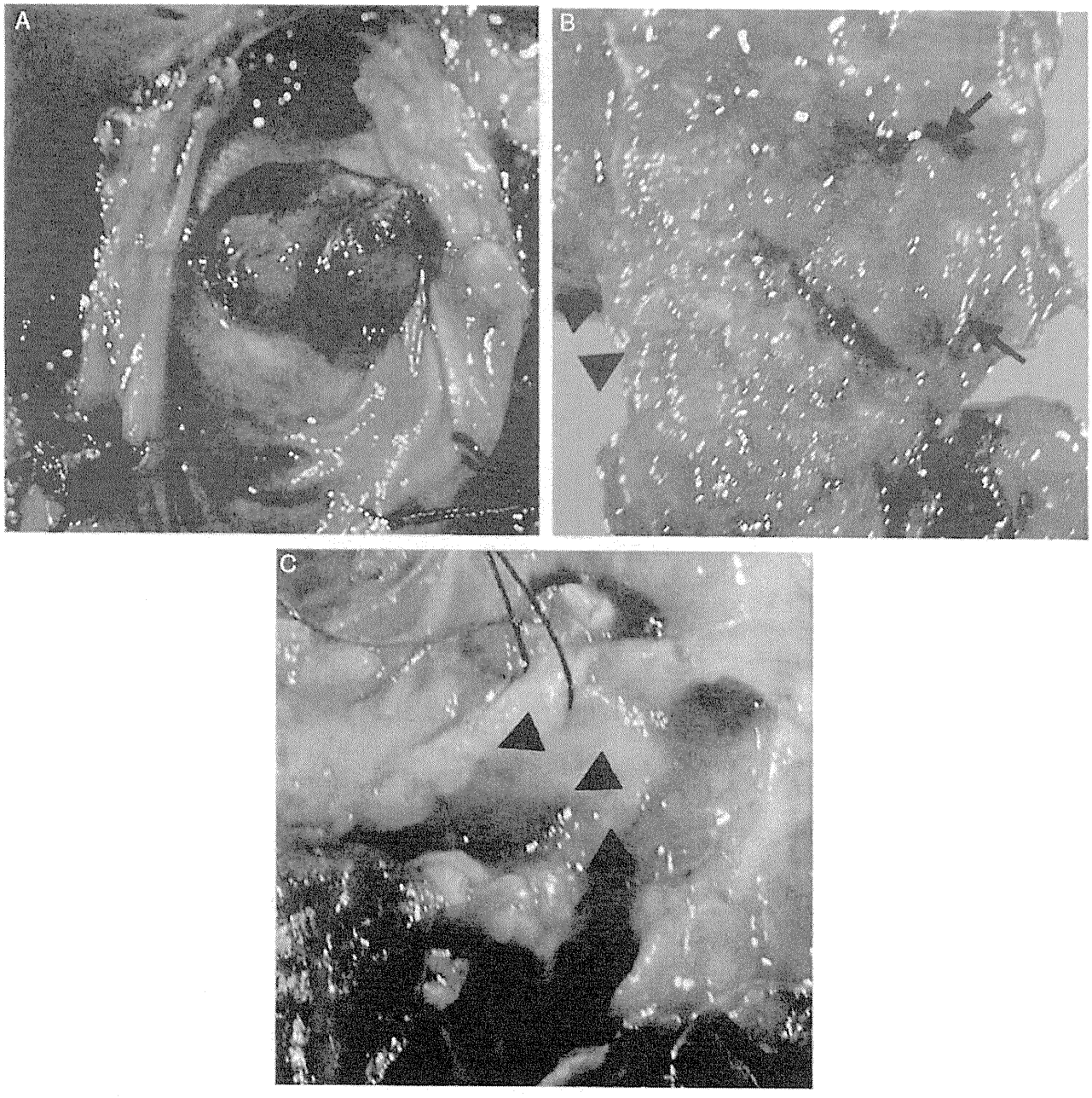

FIGURE 1. Representative images of macroscopic types of IPNB. A, Polypoid type: polypoid masses elevating into the lumen of the bile duct. B, Polypoid-granular type: main polypoid mass (arrows) with clinically visible granular or small papillary mucosa (arrowheads). C, Granular type: clinically visible granular or small papillary mucosa only (arrowheads).

the intestinal type (Fig. 2B), and 13 as the pancreatobiliary type (Fig. 2C). In 4 tumors with pancreatobiliary type, other morphologic components were concomitantly present: 2 with the intestinal component, 1 with the gastric component, and 1 with the oncocytic component (Fig. 2D). In IPNB-M, tumors of the intestinal type were significantly more common (8 of 10 tumors). Only 1 tumor seemed to be of the pancreatobiliary type and 1 was classified as the gastric type. These morphologic features were not size dependent: the average size of IPNB with gastric, intestinal, and pancreatobiliary types were 1.9, 3.2, and 2.7 cm, respectively, and these were not statistically significant.

The maximum degree of cytoarchitectural atypia of 16 IPNB-NM was characterized as carcinoma: 13 carcinomas were well differentiated and 3 were moderately differentiated. In IPNB-M, 9 tumors were diagnosed as well-differentiated papillary carcinoma. Only 1 IPNB-NM and 1 IPNB-M were characterized as papillary adenoma, which is the same disease entity as biliary papilloma. However, it was recognized that IPNB often exhibited marked variation in cytoarchitectural atypia between different regions of individual tumors. This feature was significantly more common in IPNB-M than in IPNB-NM, and 3 IPNB-NM (18%) and 8 IPNB-M (80%) showed various degrees (carcinoma, borderline, and adenoma) of cytoarchitectural atypia (Fig. 3). With regard to the relationship between cytoarchitectural atypia and histopathologic types, 10 of 11 tumors with various degrees of cytoarchitectural atypia were characterized as the intestinal type. In contrast, all but 1 tumor of the pancreatobiliary type that corresponded to carcinoma were not concomitant with any other degree of cytoarchitectural atypia ($P < 0.0001$). In a tumor of the pancreatobiliary type accompanied with another degree of cytoarchitectural atypia, a gastric component coexisted. A tumor of the intestinal type without any other degree of cytoarchitectural atypia was nonmucin producing.

Nine of 17 IPNB-NM (53%) were invasive carcinomas that extended beyond the ductal wall, whereas all but 1 IPNB-M were in situ carcinomas or minimally invasive carcinomas confined to the ductal wall. All

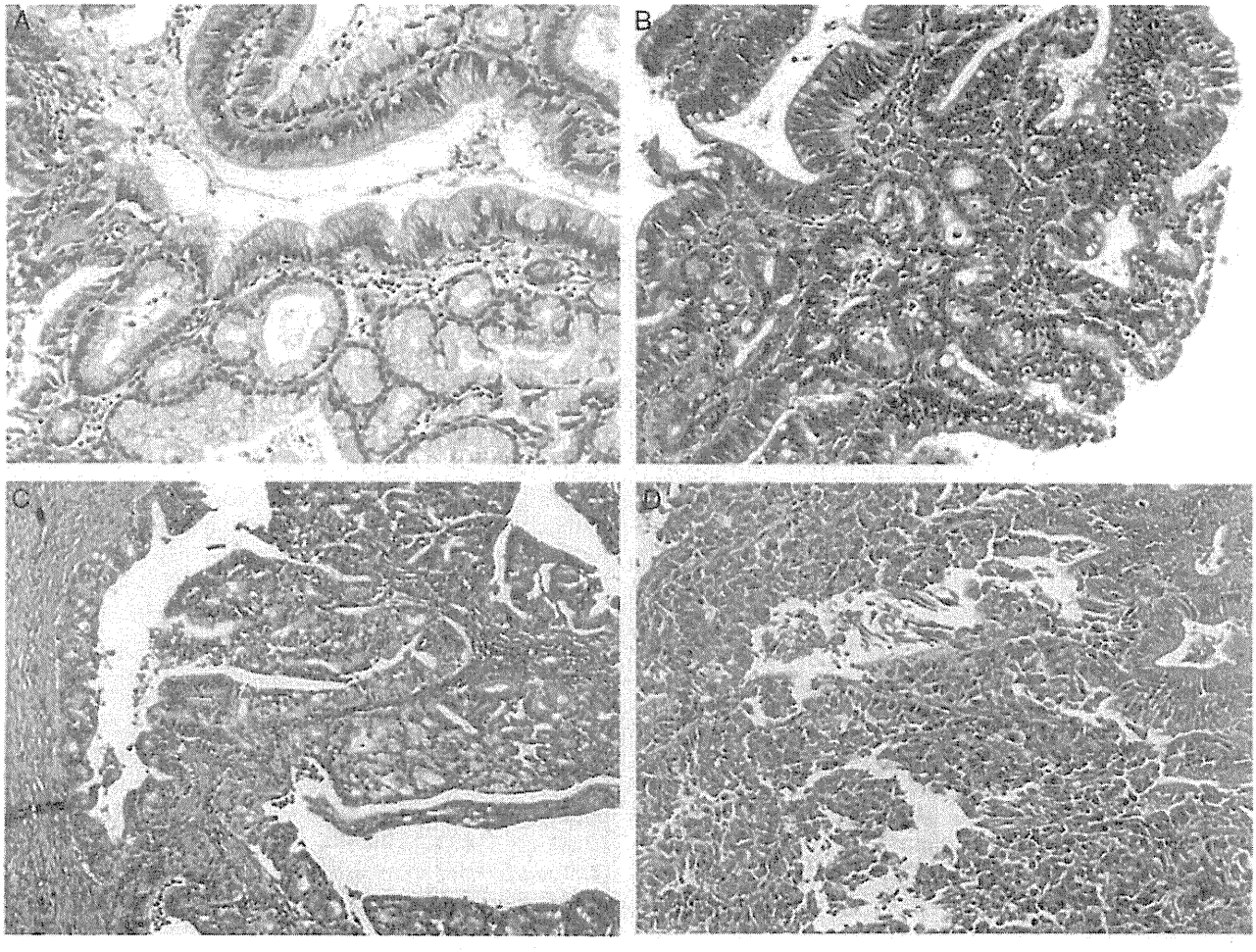

FIGURE 2. Representative images of histopathologic types of IPNB (hematoxylin and eosin staining). A, Gastric type. B, Intestinal type. C, Pancreatobiliary type. D, Oncocytic type. full color online

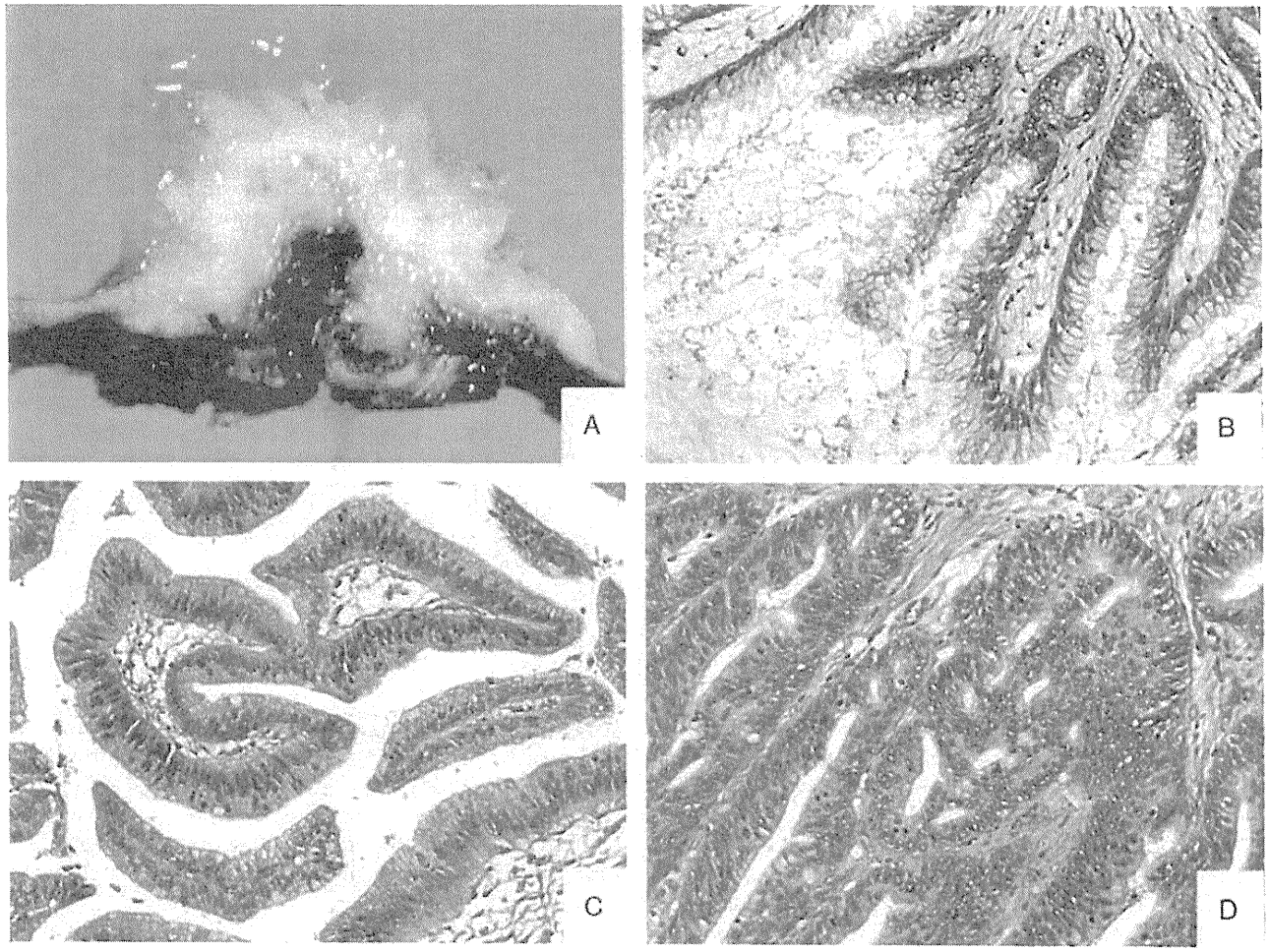

FIGURE 3. A representative case of IPNB with macroscopically visible mucin secretion. Within a single tumor (A), coexistence of adenoma (B), borderline lesion (C), or adenocarcinoma (D) was found (hematoxylin and eosin staining). full color online

IPNB-NM with invasive carcinoma exhibited tubular-type adenocarcinomas, 7 of which had infiltrating growth margin, whereas IPNB-M with invasive carcinoma showed colloid carcinoma with a pushing growth margin (Fig. 4). Lymphovascular invasion was seen within the invasion site in 6 IPNB-NM. Proliferative activity assessed by the Ki-67 labeling index was almost identical between IPNB-M and IPNB-NM. Nine of 10 IPNB with invasive carcinomas were of the pancreatobiliary type, and in IPNB of the intestinal type, only 1 tumor with mucin production showed invasion beyond the bile duct wall ($P < 0.01$).

Superficial spread along the epithelium or glands of the bile duct beyond the macroscopically detectable tumor was also observed in 3 IPNB-M and 9 IPNB-NM. This spreading pattern was generally seen in association with granular mucosa; all tumors of the polypoid-granular and granular types had this spreading pattern, whereas only 1 tumor of the polypoid type extended superficially along the bile duct. Three IPNB-NM and 1 IPNB-M showed another focus of carcinoma separated from the main mass, and were therefore considered to be multicentric. Lymph node metastasis was observed in 2 tumors without macroscopically visible mucin secretion. These pathologic features were not statistically significant between IPNB-M and IPNB-NM.

In 14 patients with IPNB-NM, ductal resected margins were free from cancer invasion, whereas no patients with IPNB-M had cancer-positive ductal resected margins.

Immunohistochemical Findings

MUC1 was expressed mainly in the apical membrane and occasionally in the cytoplasm of tumor cells. MUC2 was expressed in the cytoplasm of tumor cells. Although positive MUC2 expression was observed in only 1 case, all 10 of 10 cases with nonpapillary cholangiocarcinomas were positive for MUC1. In contrast, all but 1 IPNB-M were positive for MUC2, but positive MUC1 expression was observed in only 3 IPNB-M, including 2 with coexpression of MUC2 (Fig. 5). In cases with IPNB-NM, the frequency of positive MUC2 expression was significantly lower than in those with IPNB-M ($P < 0.01$), whereas MUC1 tended to be more

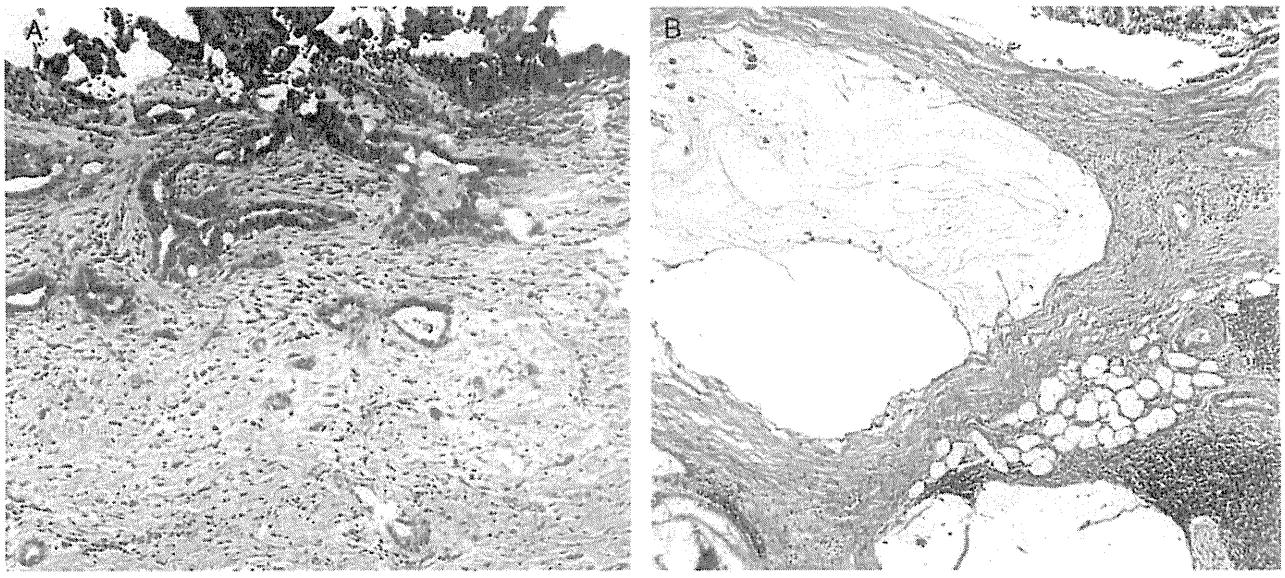

FIGURE 4. Different types of invasive carcinoma (hematoxylin and eosin staining). A, Tubular-type adenocarcinoma that developed from IPNB without macroscopically visible mucin secretion. B, Colloid carcinoma that developed from IPNB with macroscopically visible mucin secretion. full color online

frequently expressed compared with cases with IPNB-M (Fig. 6), and was expressed with similar frequency to cases with nonpapillary cholangiocarcinoma. Even 5 of 7 IPNB-NM with in situ carcinoma or minimally invasive carcinoma confined to the ductal wall showed positive MUC1 expression. Among IPNB-NM with positive MUC1 expression, 2 IPNB-NM coexpressed MUC2. Only 2 IPNB-NM showed positive MUC2 expression and negative MUC1 expression.

MUC5AC and MUC6 were expressed in the cytoplasm, and human gastric mucin was expressed in the luminal content of tumor cells. There were no statistically significant differences among IPNB-NM, IPNB-M, and nonpapillary cholangiocarcinoma as to the positive frequency of these mucin immunophenotypes. Among 4 IPNB-NM without MUC5AC expression, 3 had positive MUC1 and negative MUC2 expressions. These 3 tumors had a tubulopapillary growth pattern (Fig. 7), with a uniform degree of cytoarchitectural atypia.

All IPNB-M were negative for p53. The positivity of p53 in nonpapillary cholangiocarcinoma was significantly higher than that in IPNB-M ($P < 0.01$). The frequency of positive p53 nuclear protein in IPNB-NM was the middle level of that in IPNB-M and nonpapillary cholangiocarcinoma. Even 3 of 7 IPNB-NM with in situ carcinoma or

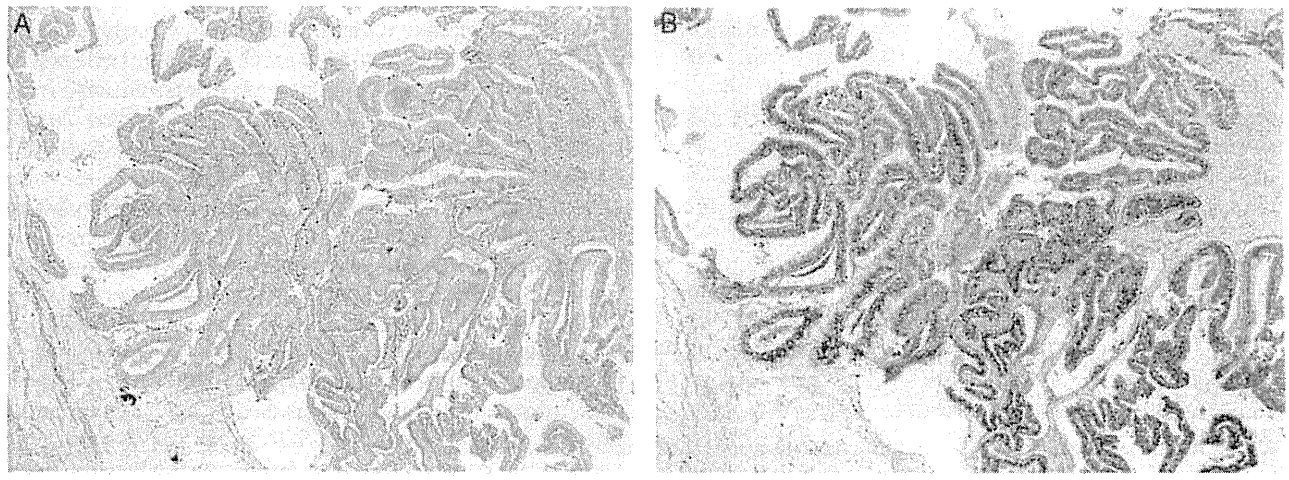

FIGURE 5. A representative pattern of the mucin immunophenotype of IPNB with macroscopically visible mucin secretion. Expression of MUC1 was negative (A) and strongly positive expression of MUC2 was observed (B). full color online

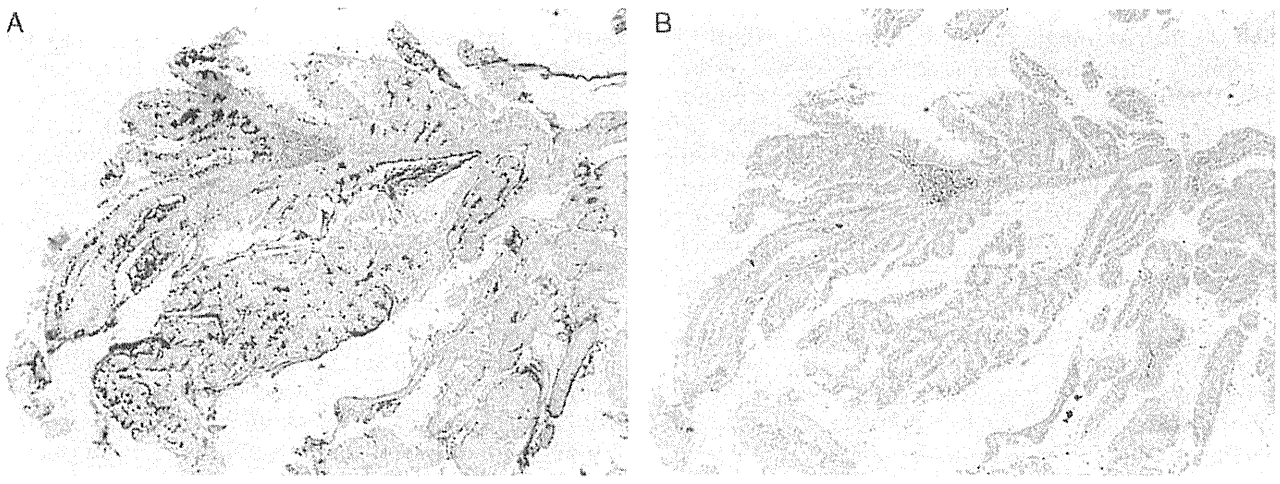

FIGURE 6. A representative pattern of the mucin immunophenotype of IPNB without macroscopically visible mucin secretion. Expression of MUC1 was observed (A) but expression of MUC2 was negative (B). full color online

minimally invasive carcinoma confined to the ductal wall showed positive p53 protein expression. Furthermore, positive p53 protein expression was observed in 2 of 3 IPNB-NM of the intestinal type.

Surgical Outcome

None of the patients with IPNB-M showed evidence of recurrent disease after a median follow-up period of 52 months (range, 12 to 80 mo). In patients with IPNB-NM, overall median survival was 31 months (range, 3 to 134 mo), and the cumulative 5-year survival rate was 49%. Six of 17 patients had died of disease 3, 11, 14, 25, 56, and 59 months after surgical resection. Among these 6 patients, 2 had invasive carcinoma with lymph node metastasis, 1 had invasive carcinoma and positive surgical margin, and 2 had invasive carcinoma. The remaining 1 patient had in situ carcinoma, but surgical margin was positive. Among the 9 patients with invasive carcinoma, overall median survival was 56 months (range, 3 to 134 mo), and the cumulative 1-year, 3-year, and 5-year survival rates were 67%, 53%, and 40%, respectively.

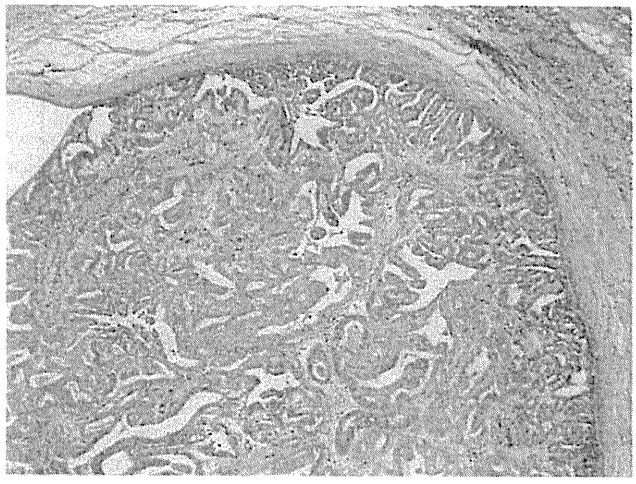

FIGURE 7. A representative image of IPNB without macroscopically visible mucin secretion that had similar characteristics to ITPNs of the pancreas (hematoxylin and eosin staining). A tubulopapillary growth pattern was indicated. full color online

DISCUSSION

Several studies have indicated radiologic and histologic similarities between IPNB-M and IPMN-P.[11,13,17,19] In our series, IPNB-M appeared as polypoid masses or granular mucosa growing into the lumen of the bile duct, with hypersecretion of mucin. Microscopically, the majority of IPNB-M was of the intestinal phenotype and showed various degrees of cytoarchitectural atypia in different regions of the individual tumors. Nine of 10 IPNB-M were less-invasive tumors confined to the ductal wall. The remaining tumor was invasive carcinoma of the colloid type. Furthermore, all but 1 IPNB-M were immunohistochemically positive for MUC2. Consistent with earlier studies, these features were very similar to those in IPMN-P reported earlier (Tables 1, 2).[2,3,6,9,14]

In contrast, pathologic findings of IPNB-NM were somewhat different from those of IPNB-M in this study, although patients with IPNB-NM resembled patients with IPNB-M in terms of clinical features. In IPNB-NM, the major histopathologic type was pancreatobiliary with a few variations in cytoarchitectural atypia. Although tumor size was almost similar between IPNB-M and IPNB-NM, the frequency of invasive carcinoma extending beyond the ductal wall was higher in IPNB-NM than in IPNB-M, suggesting that IPNB-NM was more invasive than IPNB-M, even when it is small. Furthermore, all invasive components exhibited tubular-type carcinoma. With regard to the mucin immunophenotype, the frequency of positive MUC2 expression was significantly lower in IPNB-NM than that in IPNB-M, and MUC1 was more frequently expressed. As this phenotypic pattern was also seen in IPNB-NM with noninvasive carcinoma or minimally invasive carcinoma, it was not dependent on tumor progression. These features were rather similar to those of conventional nonpapillary

cholangiocarcinoma, although IPNB-NM that had similar clinical and pathologic features to those of IPNB-M were certainly encountered, as mentioned above. Alternatively, IPNB-NM with similar characteristics (tubulopapillary growth pattern and uniform degree of cytoarchitectural atypia throughout the neoplasm) to recently proposed ITPN of the pancreas[22] were also observed. These tumors had positive MUC1 expression and negative MUC2 and MUC5AC expressions, which was the same phenotypic pattern as ITPN of the pancreas.[22]

These results were somewhat inconsistent with those provided by Zen et al,[24] in which the pathologic characteristics of biliary papillary tumors, which are in the same disease category as IPNB in this study, were compared with those of nonpapillary cholangiocarcinoma and IPMN-P. Zen et al[24] concluded that the pathologic characteristics of biliary papillary tumors were different from those of nonpapillary cholangiocarcinoma, and rather closely resembled those of IPMN-P. However, in their study, biliary papillary tumors included both IPNB-M and IPNB-NM, and the 2 types of tumor were not distinguished, possibly confusing the results. In our study, pathologic characteristics of IPNB-M resembled those of IPMN-P, whereas IPNB-NM had complex pathologic characteristics.

In terms of carcinogenesis, pancreatic carcinoma and cholangiocarcinoma develop in a stepwise progression. In the pancreas, there are 2 putative intraductal precursor lesions preceding invasive carcinoma: IPMN-P and pancreatic intraepithelial neoplasia (PanIN).[9] Although some features in both types of lesion overlap, IPMN-P commonly reach a relatively large size while remaining confined to the ducts, whereas PanIN usually progress to invasive carcinoma before they reach a significant size. At the molecular level, the *p53* gene is less frequently inactivated in IPMN-P than in PanIN.[5,8] Nuclear p53 immunohistochemical expression is reported as being more frequently observed in PanIN-3 than in carcinoma in situ in IPMN-P.[1,16] Similarly, IPNB and biliary intraepithelial neoplasia (BilIN) have recently been proposed as 2 major intraductal precursor lesions that are related to the development of invasive cholangiocarcinoma.[23,25] These lesions are probably analogous to IPMN-P and PanIN, respectively. In our study, IPNB-M did not invade beyond the bile duct wall, even when they reached a considerable size, and all IPNB-M showed negative immunohistochemical expression of p53. These findings were similar to those in IPMN-P, suggesting that IPNB-M may follow a similar carcinogenic pathway to that of IPMN-P lineage in the pancreas, and can probably develop through the IPNB carcinogenic pathway. In contrast, some IPNB-NM invaded beyond the bile duct wall while remaining smaller than IPNB-M, as mentioned above, and some IPNB-NM, even with in situ carcinoma or minimally invasive carcinoma confined to the ductal wall, showed positive p53 protein expression, which were similar findings to those in PanIN. These results suggested that some IPNB-NM, but not all, in this study might develop through a similar progressive pathway from BilIN to conventional nonpapillary cholangiocarcinoma. In the pancreas, IPMN usually arises from the main pancreatic duct or branch ducts, whereas PanIN typically involves smaller ducts. However, because in the biliary tract, both IPNB and BilIN could usually involve the same large ducts,[23,25] there may be grossly visible papillary carcinomas derived from BilIN, which is regarded as a papillary variant of conventional cholangiocarcinoma and not a subtype of IPNB.

Several studies have shown that survival rate after surgical resection in patients with IPNB were better than in patients with conventional nonpapillary cholangiocarcinoma.[10,24] This is 1 rationale for distinguishing IPNB from other types of cholangiocarcinoma. However, tumors with different backgrounds, for example, those with and without macroscopically visible mucin secretion and those with and without invasion, were combined and analyzed together in most series. In fact, survival of patients with IPNB-M was relatively favorable in this study, but invasive carcinoma that extended beyond the ductal wall was presented in only 1 case. In contrast, although only a small sample was evaluated, the survival of patients with invasive IPNB-NM was similar to that of patients with bile duct cancer in an analysis based on a large number of patients.[15]

In conclusion, IPNB-M showed striking similarities to IPMN-P in its clinical, morphologic, immunophenotypical, and biological findings. In contrast, IPNB-NM contained heterogeneous disease groups; some tumors had similar characteristics to IPNB-M and IPMN-P, some had the characteristics resembled in those of ITPN of the pancreas, and the majority of IPNB-NM had the characteristics close to those of nonpapillary cholangiocarcinoma. The concept of IPNB as a biliary counterpart of IPMN-P is attractive, but these findings suggest that it may be difficult to assume that all IPNB-NM are included in this disease entity with IPNB-M. Further study with a large number of cases, especially on the basis of a molecular analysis, is required to assess which tumors among IPNB-NM could be categorized to the tumors of the IPNB lineage.

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（分担研究報告書）

がん診療ガイドラインの作成（新規・更新）と公開の維持および その在り方に関する研究

（研究分担者　中尾昭公・名古屋セントラル病院・院長）

研究要旨
膵癌診療ガイドラインは初版(2006年)、第2版(2009年)を出版・改訂し、2012年度には第3版の出版を予定している。ガイドラインの評価を検証し、問題点や課題を考察し今後の改訂作業に反映していく。

A．研究目的
第2版ガイドラインの評価を検証し、問題点や課題を考察する。またガイドラインのWeb化へ向けた資料作成を行う。

B．研究方法
ガイドライン作成に直接関わっていない膵癌外科系専門医2名、臨床ガイドラインに精通している非専門医1名、生物統計学専門家1名、患者代表1名の計5名から構成される外部評価委員により独立した評価を行った。評価はAGREE、Shaneyfelt、COGSによる評価法を用いた。

（倫理面への配慮）該当なし。

C．研究結果
1. AGREEによる評価は:1)対象と目的2)利害関係者の参加 3)作成の厳密さ 4)明確さと提示の仕方 5)適用可能性 6)編集の独立性の6領域から成る23項目と全体評価1項目の計24項目による。評価の結果「利害関係者の参加」について改善の余地があることが示唆された。各項目に関しては「臨床上の問題が具体的に記載されている」「エビデンスの選択基準が明確に記載されている」「公表の前に外部審査がなされている」「改訂が予定されている」などが高評価を得た。一方で評価が低かった項目は「患者の価値観や好みが十分に考慮されている」「患者の状態に応じて可能な他の選択肢が明確に示されている」などであった。

2. Shaneyfeltらによる評価は25項目、全てYes/Noで回答する。「ガイドラインの目的の明確性」などが高評価である一方「利得と害が定量的に記載されている」「診療行為のコストへの影響が記載されている」などについてYesの回答は少なかった。

3. COGSによる評価法は18項目、Yes/No回答方式である。「概観資料(構造化抄録の提示等)」や「焦点(扱う主な疾患についての記載等)」などの項目が高評価を得た。

D．考察
評価の結果、ガイドラインの対象や目的、作成プロセス、推奨(勧告)の明確さなどについてはいずれの評価方法でも高い評価が得られたものの、利害関係者の参加、適用可能性などについては評価が低い。これらをどう考慮していくか今後の課題である。AGREEによる全体評価では評価者全員が「有用」と回答した。ShaneyfeltやCOGSでは医学部全体評価はないものの、全項目をまとめて全体でのYesと回答した割合を試験的に求めてみたところ、80%以上であり、課題は残るものの総じて高評価を得たと考えられる。

E．結論
ガイドラインを実際の臨床現場で用いられることを目的としているので、より多くの医師、コメディカル、患者などからの評価を受け、意見を求めることが重要である。またどのような評価方法を用いるのかについても今後検討が必要である。

F．健康危険情報
（分担研究報告書には記入せずに、総括研究報告書にまとめて記入）

G．研究発表
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Yamaguchi K, et al: EBM-based Clinical Guidelines for Pancreatic Cancer 2009 From the Japan Pancreas Society: A Synopsis. Jpn J Clin Oncol 2011;41:836-840, 2011
2.　学会発表
該当なし。
（発表誌名巻号・頁・発行年等も記入）

H．知的財産権の出願・登録状況
（予定を含む。）
1. 特許取得
該当なし。
2. 実用新案登録
該当なし。
3. その他

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(7)836–840
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Review Article

EBM-based Clinical Guidelines for Pancreatic Cancer 2009 From the Japan Pancreas Society: A Synopsis

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Clinical Practice Guidelines for Pancreatic Cancer Based on Evidence-based Medicine, 2006, were published by the Japan Pancreas Society (Committee for Revision of Clinical Guidelines for Pancreatic Cancer) in March 2009 in Japanese[1] and were revised to Clinical Practice Guidelines for Pancreatic Cancer Based on Evidence-based Medicine 2009 in July 2009 in Japanese.[2] These guidelines were established according to Evidence-Based Medicine. A total of 443 papers were collected from 2544 reports concerning pancreatic cancer that were listed on PubMed and Igakuchuo Zasshi from July 2004 to April 2007. This new guidelines were written by members of the Committee for Revision of Clinical Practice Guidelines for Pancreatic Cancer in the Japan Pancreas Society. The guidelines show algorithm for the diagnosis (Fig. 1) and treatment (Fig. 2) of pancreatic cancer, address five subjects: diagnosis, chemotherapy, radiation therapy, surgical therapy and adjuvant therapy, and include 25 clinical questions (CQs) and 39 recommendations. The corresponding CQ numbers are inserted in the algorithms. There are five degrees of recommendation:

A Strongly recommended because there is strong scientific evidence.
B Recommended because there is scientific evidence.
C1 Recommended although there is no scientific evidence.
C2 Not recommended because there is no scientific evidence.
D Not recommended because there is evidence showing that it is ineffective or harmful.

This article presents a synopsis of the guidelines in English.

Diagnosis

CQ1-1 What are risk factors for pancreatic cancer?

The below-mentioned risk factors have been reported to have evidences supporting the relationship between the factors and pancreatic cancer:

(i) Family history: pancreatic cancer and hereditary pancreatic cancer syndrome.
(ii) Accompanying diseases: diabetes mellitus, obesity, chronic pancreatitis, hereditary pancreatitis, intraductal papillary mucinous neoplasm (IPMN).
(iii) Habits: tobacco.

RECOMMENDATION 1-1

(i) Patients with more than one risk factor are recommended to undergo further examination to detect pancreatic cancer (Grade B).
(ii) IPMN progresses to invasive cancer and accompanies pancreatic cancer. IPMN should be adequately assessed and carefully followed up (Grade B).

CQ1-2 What are the clinical symptoms of pancreatic cancer?
The below-mentioned clinical symptoms have been reported as those of pancreatic cancer:

(i) Abdominal pain is the most frequent symptom, followed by jaundice, back pain and body weight loss.
(ii) Clinically silent pancreatic cancer.
(iii) Fifty percent of pancreatic cancer patients show early-onset diabetes mellitus (glycogen metabolism disturbance) within 3 years.

RECOMMENDATION 1-2

(i) Patients with unexplainable abdominal pain, back pain, jaundice and/or body weight loss should undergo further examination for pancreatic cancer. However, the clinical outcome of symptomatic pancreatic cancer is poor (Grade B).

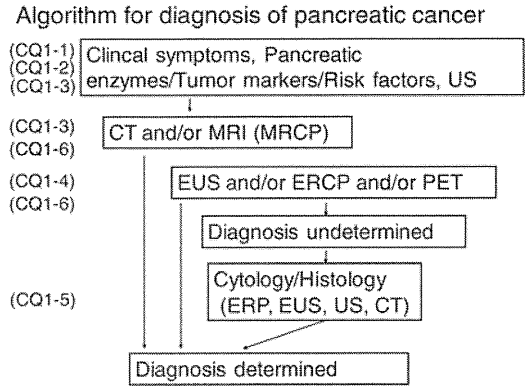

Figure 1. Algorithm for diagnosis of pancreatic cancer.

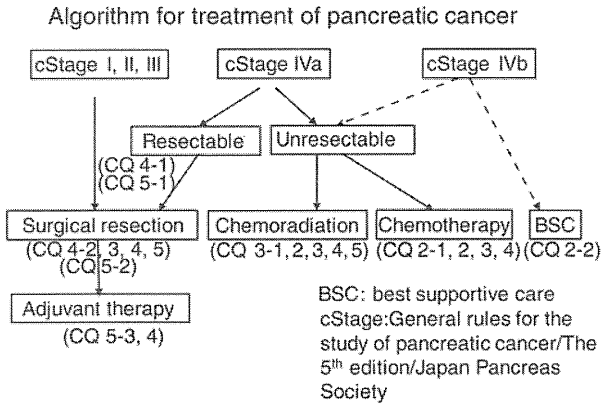

Figure 2. Algorithm for treatment of pancreatic cancer.

(ii) Early-onset diabetes mellitus (poor glycogen metabolism) and deterioration of diabetes mellitus suggest the presence of pancreatic cancer and necessitate further examination for pancreatic cancer (Grade B). Early-onset diabetes mellitus (within less than 3 years) may indicate pancreatic cancer.

CQ1-3 What is the first step when pancreatic cancer is suspected?

The below-mentioned examinations are the first-step diagnostic procedures of pancreatic cancer:

(i) Serum pancreatic enzyme
(ii) Tumor markers
(iii) Ultrasound (US)
(iv) Computed tomography (CT).

RECOMMENDATION 1-3

(i) The serum pancreatic enzyme level is important, but is not specific for pancreatic cancer (Grade C1).
(ii) Serum tumor makers including CA19-9 are recommended for the diagnosis of pancreatic cancer and follow-up of pancreatic cancer (Grade B), but they are not useful for the diagnosis of early pancreatic cancer.
(iii) US is recommended for the first screening for pancreatic cancer (Grade B) but has a low rate of detecting pancreatic cancer (Grade C1). Dilatation of the main pancreatic duct or a pancreatic cyst is an important indirect sign of pancreatic cancer (Grade B). Further examination, including CT, is therefore strongly recommended if such signs are evident (Grade A).
(iv) Patients the abnormal findings listed above should be periodically examined and careful follow-up is recommended if no diagnosis of pancreatic cancer obtained (Grade B).

CQ1-4 What is the second step when pancreatic cancer is suspected?

RECOMMENDATION 1-4

(i) Qualitative diagnosis is important and is strongly recommended to determine the treatment of pancreatic cancer (Grade A).
(ii) US and CT (enhancing) should be performed and additional examination by magnetic resonance cholangiopancreatography, endoscopic ultrasound (EUS), ERP or positron emission tomography is strongly recommended when necessary (Grade A).

CQ1–5 What is the significance and indications for cytology and biopsy of pancreatic cancer?

RECOMMENDATION 1-5

(i) Either a histological or cytological diagnosis is recommended before treatment started if no qualitative diagnosis of pancreatic mass obtained. Aspiration cytology or histology with US guidance, cytology or histology under endoscopic ultrasonography, pancreatic juice cytology under endoscopic retrograde cholangiopancreatography (ERCP) or histology under ERCP should be obtained to achieve a definite diagnosis, depending on the patients or institution (Grade B).
(ii) Aspiration cytology under endoscopic ultrasonography is useful when the lesion is not detected by ultrasonography or CT (Grade C1).
(iii) A genetic analysis is important to confirm the cytology or histology (Grade C1).

CQ1-6 How do you determine clinical staging of pancreatic cancer?

RECOMMENDATION 1-6

Multidetector CT or EUS is recommended for staging diagnosis (TNM) of pancreatic cancer (Grade B).

Chemotherapy

CQ2-1 Is chemotherapy alone recommended for locally advanced unresectable pancreatic cancer?

RECOMMENDATION 2-1

Chemotherapy alone is recommended as one of options for the treatment of locally advanced unresectable pancreatic cancer (Grade B).

CQ2–2 What is the first-line chemotherapy for metastatic pancreatic cancer?

RECOMMENDATION 2-2

Gemcitabine (GEM) is recommended as the first-line treatment for metastatic pancreatic cancer (Grade A).

CQ2-3 How long is GEM continued for unresectable pancreatic cancer?

RECOMMENDATION 2-3

GEM is continuously administered for unresectable pancreatic cancer until clear progression becomes evident if there are no adverse effects causing interruption of the administration of GEM (Grade B).

CQ2-4 Is second-line chemotherapy recommended for unresectable pancreatic cancer?

RECOMMENDATION 2-4

There is no scientific evidence of effective second-line chemotherapy within the insurance allowance in this country, but some reports suggest effectiveness. Some recent randomized clinical trials in other countries have reported effective second-line chemotherapy. Second-line chemotherapy can be considered in patients whose physical status is good and are fully informed after a detailed explanation (Grade C1).

Radiotherapy

CQ3-1 Is chemoradiation effective for locally advanced unresectable pancreatic cancer?

RECOMMENDATION 3-1

Chemoradiation is effective for locally advanced unresectable pancreatic cancer and is recommended as one of the options for treatment (Grade B).

CQ3-2 What is the standard combined chemotherapy for chemoradiation for locally advanced unresectable pancreatic cancer?

RECOMMENDATION 3-2

5-fluorouracil (5-FU) (Grade B) is the standard chemotherapy for chemoradiation for locally advanced pancreatic cancer.

Although there is no definite evidence supporting GEM-based chemoradiation, some report its usefulness. A safe regimen of GEM-based chemoradiation can be considered as one of the options for treatment after the procedure is fully explained and the patient provides informed consent (Grade C1).

CQ3-3 Is the lymph node included in the clinical standard field of external radiation therapy for locally advanced unresectable pancreatic cancer?

RECOMMENDATION 3-3

There have been no prospective randomized clinical trials concerning this CQ. Radiation including the tumor and the positive lymph nodes in the radiation field is recommended prophylactically, although there is no supportive scientific evidence (Grade C1).

CQ3-4 Is intraoperative radiation effective for locally advanced pancreatic cancer?

RECOMMENDATION 3-4

There are reports of the efficacy of intraoperative radiation for locally advanced unresectable pancreatic cancer. However, there is no scientific evidence that intraoperative radiation improves the clinical course of locally advanced unresectable pancreatic cancer (Grade C1).

CQ3-5 Does chemoradiation improve the quality of life of patients with unresectable pancreatic cancer?

RECOMMENDATION 3-5

Cancer radiation therapy (Grade C1) and chemotherapy (Grade B) are therefore recommended to improve the quality of patients with unresectable pancreatic cancer.

Surgical therapy

CQ4–1 Is surgical resection useful for Stage IVa pancreatic cancer?

RECOMMENDATION 4-1

Surgical resection with an intended curative resection is recommended for pancreatic cancer up to Stage IVa* (Grade B).

Stage IVa*: Stage IVa indicates (S2 or R2 or PV2) and (N0 or N1) by Japan Pancreas Society Classification of pancreatic cancer, 4th Edition.

CQ4–2 Is preservation of the stomach useful in pancreatoduodenectomy for pancreatic head cancer?

RECOMMENDATION 4-2

It is not clear whether preservation of the stomach improves the rate of post-operative complications, quality of life, post-operative pancreatic function and nutrition status of patients with pancreatic cancer or not (Grade C1).

Preservation of the stomach decreases the operation time and blood loss in pancreatoduodenectomy but does not decrease the survival rate after a surgical resection (Grade C1).

CQ4-3 Does combined portal vein resection improve the clinical outcome of patients with pancreatic head cancer?

RECOMMENDATION 4-3

The effect of prophylactic portal vein resection intended to increase the curability on the clinical course of patients with pancreatic cancer is unclear. A portal vein resection is indicated when surgical and dissection margins can be free from cancer cells by portal vein resection (Grade C1).

CQ4-4 Is a radical resection with extended lymph node dissection useful for pancreatic cancer?

RECOMMENDATION 4-4

The contribution of extended lymph node and nerve plexus dissection to the improvement of clinical course of patients with pancreatic cancer is unclear and there is no evidence to support the performance of such an extended radical resection (Grade C2).

CQ4-5 Is the incidence of complications after pancreas resection low in a high volume center?

RECOMMENDATION 4-5

The incidence of complications tends to be low in pancreatic surgery including pancreatoduodenectomy and the management of complications tends to be superior in institutions with a high volume of pancreatic surgery (Grade B).

CQ4-6 Is surgical bypass or biliary stent significant in unresectable pancreatic cancer?

RECOMMENDATION 4-6

Hepaticojejunostomy for the obstructive jaundice and prophylactic gastrojejunostomy is recommended in patients with unresectable obstructive jaundice after laparotomy (Grade B).

Adjuvant therapy

CQ5-1 Does pre-operative therapy improve the clinical outcome of patients with pancreatic cancer?

RECOMMENDATION 5-1

There is increasing evidence supporting the efficacy of pre-operative treatment [(i) chemoradiation and (ii) chemotherapy]. However, clinical trials or analyses of the long term are required to determine whether such therapy improves the clinical outcome (Grade C1).

CQ5-2 Is intraoperative radiation therapy recommended at the time of resection of pancreatic cancer?

RECOMMENDATION 5-2

There has been no definite evidence supporting the usefulness of intraoperative radiotherapy. However, clinical trials or analyses of the long term are required to determine whether such therapy improves the clinical outcome (Grade C1).

CQ5-3 Is post-operative chemoradiation recommended for pancreatic cancer?

RECOMMENDATION 5-3

Meta-analysis of 5-FU-based post-operative chemoradiation revealed no supportive evidence. However, clinical trials or analyses of the long term are required to determine whether GEM-based post-operative chemoradiation improves the clinical outcome (Grade C1).

CQ5-4 Is post-operative adjuvant therapy recommended for pancreatic cancer?

RECOMMENDATION 5-4

There is no definite international consensus on post-operative adjuvant therapy. Post-operative GEM is safe and effective and is recommended as post-operative chemotherapy (Grade B).

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(Nagoya University). *Adjuvant therapy*: O. Ishikawa (Osaka Medical Center for Cancer and Cardiovascular Diseases), T. Okusaka (National Cancer Center) and T. Shimosegawa (Tohoku University).

Conflict of interest statement

None declared.

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がん診療ガイドラインの作成(新規・更新)と公開の維持およびその在り方に関する研究

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研究要旨
膵・消化管神経内分泌腫瘍(NET)は比較的稀な疾患である。悪性腫瘍であるにもかかわらず、カルチノイドなどの名称で呼ばれたこともあり、未だに良性腫瘍として経過観察されることが多く、初診時に約半数が肝転移を伴った状態で見つかる状況である。外科的切除と薬物療法で治療されるが、早期診断・早期切除が最善の治療法である。本邦での、NETに対する知識は普及しているといえず、国際的に承認され普及している診断技術と治療薬の本邦での承認も遅れている現状にある。最近、国内での治療薬の臨床試験が始まり、新規の分子標的薬の有効性が国際的臨床試験で明らかにされて国内への導入も進んできている。本邦での患者数の増加を認めており、NET診療技術が急速に進歩している現在、NETの診断と治療に関するガイドラインが強く求められている。本邦での臨床的NET研究が熱心な臨床家と病理医などの努力で進んでいて、国内での知見が集積されてきた。それらを基礎にして、本邦で先進的なNET診療ガイドライン作成作業が着実に進行している。

A．研究目的

25人以上の膵・消化管NETを専門とする臨床医師と病理医師、患者さん代表が集まり、現時尼での論文発表を検索して、科学的に臨床的設問に対する推奨を示す膵・消化管NET診療ガイドラインを作成することを目的とする。

B．研究方法

膵・消化管NETの診療に際して、実地医家が患者さん本位の診療をする際に必要で、かつ重要な設問を設定し、それに対する推奨できる解答を作成するのであるが、その際過去になされた臨床的研究の成果をNPO法人日本医学図書館協会に受託して検索する。その評価を診断、外科的治療、内科的治療、MEN関係病理などの各小委員会で行う。各小委員会で作成した臨床的設問と解答を全体委員会で討議してガイドライン案を作成し、公開し、公聴会を消化器外科学会、内分泌外科学会などで開き、そこでの質疑を勘案してガイドラインを完成させ、出版する予定である。癌治療学会での評価委員会を経てHome Page 上も公開を考えている。

(倫理面への配慮)

患者さんを含む評価委員会で検討してもらって、倫理面変配慮する意向である。

C．研究結果

今年度は、臨床的設問を既に作成し、現在文献検索を終えて、推奨的意見のまとめをしている段階である。

D．考察

今年度は、「膵・消化管神経内分泌腫瘍〇（NET）診断・治療実践マニュアル」という膵・消化管ＮＥＴに関するまとまった教科書を本ガイドライン作成員を中心的著者とする執筆陣で出版することができた。この過程で考察したことがガイドライン作成にも行かせる経験であった。各委員もＮＥＴに関する研究発表を行い、国際的学会でも発表して、本邦でのガイドライン作成の準備を続けている。一方で、本邦では、ＮＥＴの診療で国際的に承認済みの抗がん薬や検査法と検査薬の承認が遅れておりその改善を目指した活動が始まり、進んでいる。

E．結論

膵・消化管NETの診療に際して必須の検査法と治療薬、検査薬の承認が実現できることが望まれ、それによりガイドライン作成も円滑に進むと考えている。

F．健康危険情報

特になし

G．研究発表

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Review Article

Surgical Management of Pancreatic Neuroendocrine Tumors

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Abstract
This study outlines the surgical management and clinicopathological findings of pancreatic neuroendocrine tumors (P-NETs). There are various surgical options, such as enucleation of the tumor, spleen-preserving distal pancreatectomy, distal pancreatectomy with splenectomy, pancreatoduodenectomy, and duodenum-preserving pancreas head resection. Lymph node dissection is performed for malignant cases. New guidelines and classifications have been proposed and are now being used in clinical practice. However, there are still no clear indications for organ-preserving pancreatic resection or lymph node dissection. Hepatectomy is the first choice for liver metastases of well-differentiated neuroendocrine carcinoma without extrahepatic metastases. On the other hand, cisplatin-based combination therapy is performed as first-line chemotherapy for metastatic poorly differentiated neuroendocrine carcinoma. Other treatment options are radiofrequency ablation, transarterial chemoembolization/embolization, and liver transplantation. Systematic chemotherapy and biotherapy, such as that with somatostatin analogue and interferon-α, are used for recurrence after surgery. The precise surgical techniques for enucleation of the tumor and spleen-preserving distal pancreatectomy are described.

Key words Neuroendocrine tumor · Enucleation · Spleen-preserving pancreatectomy · Surveillance

Introduction

Pancreatic neuroendocrine tumors (P-NETs) are comparatively rare neoplasms, and account for only 1%–2% of all pancreatic neoplasms. The incidence of P-NETs is approximately 1 per 100000 people.[1–5] The incidence in autopsy cases ranges from 0.26% to 1.4%.[6,7] An autopsy study of 800 elderly subjects cut specimens every 5mm and found tiny neuroendocrine tumors in more than 10% of the cases.[8]

Pancreatic neuroendocrine tumors include benign neoplasms without metastasis or invasion, as well as high-grade malignant neoplasms. The assessment of tumor malignancy is important for determining the surgical strategy for P-NETs. The World Health Organization states that pancreatic neuroendocrine tumors can be classified into three categories (well-differentiated neuroendocrine tumor, well-differentiated neuroendocrine carcinoma, and poorly differentiated neuroendocrine carcinoma) based on the presence or absence of metastasis, direct invasion, arterial or venous invasion, perineural invasion, hormonal syndrome, the size of the tumor, histological differentiation, and Ki-67 index[9] (Table 1). Well-differentiated neuroendocrine tumors are also classified based on benign or uncertain behavior.

Small P-NETs such as insulinoma, which are usually categorized into benign behavior of well-differentiated neuroendocrine tumor, are typically solid and hypervascular tumors. Cystic changes due to cystic degeneration, necrosis, and hemorrhage are seen with both well-differentiated neuroendocrine tumors and well-differentiated neuroendocrine carcinomas.[10,11]

The European Neuroendocrine Tumor Society proposed guidelines for the treatment and prognostic stratification of gastroenteropancreatic neuroendocrine tumors in 2006 by histological differentiation according to the WHO classification, the TNM (Tumor–Nodes–Metastasis) classification (Table 2), and grading based on the proliferative activity, such as the Ki-67 labeling index and mitotic count[12,13] (Tables 3 and 4).

The American Joint Committee on Cancer (AJCC) proposed a new TNM classification for P-NETs in 2009.[14] This classification is used for pancreatic ductal

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adenocarcinoma; the AJCC applied the same classification for P-NETs (Table 5). There are two major differences between the AJCC-TNM classification and the European Neuroendocrine Tumor Society (ENETS)-TNM classification: the definition of the T stages and the consideration of tumor grading based on proliferative activity. Both TNM classifications are effective prognostic indicators.[15–19] However, they are not free of problems.[20,21] The fact that there are two TNM classifications actually causes confusion among many practitioners. Further studies on clinicopathological data and clinical application methods will lead to a unified TNM classification. This article describes the surgical options for the treatment of pancreatic neuroendocrine tumors.

Table 1. Criteria for the clinicopathological classification of pancreatic endocrine tumors[9]

1	Well-differentiated endocrine tumor
1.1	"Benign" behavior Confined to the pancreas, non-angioinvasive, no perineural invasion, <2 cm in diameter, <2 mitoses/10 HPF, <2% Ki-67-positive cells
1.2	Uncertain behavior Confined to the pancreas and one or more of the following features: ≥2 cm in diameter, 2–10 mitoses/10 HPF, >2% Ki-67-positive cells, angioinvasion, perineural invasion
2	Well-differentiated endocrine carcinoma Low grade malignant Gross local invasion and/or metastases
3	Poorly differentiated endocrine carcinoma High grade malignant >10 mitoses/10 HPF

HPF, high-power fields

Surgical Strategies for P-NETs

Surgical treatment for P-NETs varies according to the site and size of the tumor, and whether it is single or multiple, benign or malignant, and associated with multiple endocrine neoplasia (MEN) type 1 or not. Patients with nonfunctioning P-NETs smaller than 1.0 mm, which are occasionally found at autopsy, are certainly not candidates for treatment. Approximately 70%–90% of

Table 3. A grading system for neuroendocrine tumors proposed by the European Neuroendocrine Tumor Society[13]

Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

[a] 10 HPF: high-power field = 2 mm², at least 40 fields, evaluated in areas at highest mitotic density
[b] MIB 1 antibody: Percentage of 2000 cells in areas of highest nuclear labeling

Table 2. TNM classification and disease staging for neuroendocrine tumors of the pancreas proposed by the European Neuroendocrine Tumor Society[13]

Abbreviation	Characteristics			
T — primary tumor				
TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumor			
T1	Limited to the pancreas and size <2 cm			
T2	Limited to the pancreas and size 2–4 cm			
T3	Limited to the pancreas and size >4 cm or invading duodenum or bile duct			
T4	Invading the wall of adjacent large vessels (celiac axis or superior mesenteric artery), stomach, spleen, colon, adrenal gland			
	For any T add (m) for multiple tumors			
N — regional lymph nodes				
NX	Regional lymph node status not assessed			
N0	Absence of lymph node metastasis			
N1	Presence of regional lymph node metastasis			
M — distant metastases				
MX	Distant metastasis not assessed			
M0	Absence of distant metastases			
M1	Distant metastasis			
Stage		T	N	M
I		T1	N0	M0
IIa		T2	N0	M0
IIb		T3	N0	M0
IIIa		T4	N0	M0
IIIb		Any T	N1	M0
IV		Any T	Any N	M1

Table 4. Proposal for the stratification of gastroenteropancreatic neuroendocrine tumors into three treatment groups based on growth features, TNM stages, and grade[13]

Prognosis	Histological type	Grade	Stage	Potential treatment
Localized tumor				
Very low risk of metastasis	Well differentiated	G1	T1	Endoscopic resection
Low risk	Well differentiated	G1	T2	Surgery
Intermediate risk	Well differentiated	G2	T1	Surgery
High risk	Well differentiated	G1/2	T2	Surgery
High risk	Poorly differentiated	G3	T1/2/3	Surgery, AT
Nodal metastases				
Slow growth	Well differentiated	G1	T1/2/3 N1	Surgery
Intermediate growth	Well differentiated	G2	T1/2/3 N1	Surgery, AT
Fast growth	Poorly differentiated	G3	T1/2/3 N1	Surgery, AT
Nodal and hematogenous metastases				
Slow growth	Well differentiated	G1	Any T N1 M1	Surgery, AT
Intermediate growth	Well differentiated	G2	Any T N1 M1	Surgery, AT
Fast growth	Poorly differentiated	G3	Any T N1 M1	Chemotherapy

AT: additional treatment, including biotherapy and/or chemotherapy

Table 5. Definition of TNM proposed by the American Joint Committee on Cancer[14]

Abbreviation	Characteristics
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension
T2	Tumor limited to the pancreas, >2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
—	
M0	No distant metastasis
M1	Distant metastasis

Stage	T	N	M
0	T0	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

enlarging P-NETs have malignant features, such as invasion and metastases.[21–23] However, there are no definite indications regarding whether functioning and nonfunctioning P-NETs should be removed or observed based on size, since P-NETs are so rare that there is little evidence indicating the size of tumors that should be treated.[24–26]

Criteria for the clinicopathological classification of P-NETs as defined by the World Health Organization (WHO) classification have been published and applied in clinical practice (Table 1).[9] Functional P-NETs such as insulinoma and gastrinoma are treated surgically, even if the tumor is smaller than 1 cm. Despite the small size, gastrinoma has malignant potential.[27,28] By contrast, nonfunctioning P-NETs are observed if the tumor is smaller than 1 cm. This size is arbitrary, so careful follow-up and further investigations are needed.[24,26,28–31]