Risk of Malignancy Using the Diagnostic Categories Proposed by the World Health Organization International System for Reporting Pancreaticobiliary Cytopathology

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Abstract

\textbf{Background:} The World Health Organization (WHO) proposed an updated reporting system for pancreaticobiliary cytology, which moves low-grade malignancies to “positive for malignancy” group and serous cystadenoma to “negative for malignancy” group. The WHO system also created two new categories, namely, pancreatic neoplasia-low grade (PaN-Low) and pancreatic neoplasia-high grade (PaN-High), which includes neoplastic mucinous cysts and stratifies them according to their cytologic atypia. The risk of malignancy (ROM) of the new categories of the WHO system needs to be defined.

\textbf{Methods:} Cytologic slides of all patients, who underwent endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) biopsy at our institution from January 2010 to December 2021 and had a histopathological or clinical follow-up of at least 6 months, were reviewed and reclassified under the Papanicolaou Society of Cytopathology (PSC) and WHO reporting systems. The absolute ROM was calculated for each category of both reporting systems.

\textbf{Results:} A total of 420 EUS-FNA samples from 410 patients were reviewed and reclassified. The absolute ROM for the proposed WHO system was 35\% for “nondiagnostic,” 1.0\% for “negative for malignancy,” 69.0\% for “atypical,” 11\% for “PaN-Low,” 100\% for “PaN-High,” 91\% for “suspicious for malignancy,” and 100\% for “malignant.” Comparatively, the absolute ROM under the PSC reporting system was 34\% for “nondiagnostic,” 1.0\% for negative (for malignancy), 50.0\% for “atypical,” 0.0\% for “neoplastic: benign,” 16\% for “neoplastic: other,” 88\% for “suspicious for malignancy,” and 100\% for “positive or malignant.”

\textbf{Conclusion:} The proposed WHO international reporting system has advantages regarding risk stratification improvement and case management.

Introduction

Pancreatic cancer is one of the solid tumors with the worst prognosis and is currently the seventh leading cause of cancer-associated death worldwide with a 5-year survival rate of $<10\%$ [1]. Cystic and/or solid pancreatic le-
lations can be either benign, premalignant, or malignant [2, 3]. An accurate and timely preoperative diagnosis is extremely important for appropriate patient management. Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) biopsy of the pancreas is a minimally invasive, safe, and accurate diagnostic test, with high sensitivity and specificity in evaluating pancreatic solid and cystic masses [1, 3–7]. Aspirated material can be effectively triaged for cytomorphic examination and biochemical and molecular tests for accurate diagnosis [8]. Pancreatic lesions’ diagnosis and therapy is a multidisciplinary team-work including radiologists, endoscopists, pathologists, surgeons, and medical and radiation oncologists. Clear communication among the members of this team is of high importance for timely and accurate patient management [2, 9]. Standardized reporting systems in cytology, which have been used worldwide over the last decade, such as the Bethesda System for Reporting Thyroid Cytology, Paris System for Urinary Cytology, and Milan System for Salivary Gland Cytology, improved the communication between cytopathologists and clinicians [10–12]. The Papanicolaou Society of Cytopathology (PSC) published guidelines for reporting pancreaticobiliary cytology in 2014 [9] and an Atlas in 2015 [13]. The PSC for Reporting Pancreaticobiliary Cytology classifies pancreaticobiliary samples into six categories as follows: I, nondiagnostic; II, negative for malignancy; III, atypical; IV, neoplastic (consisting of two subcategories as IVB, neoplastic-benign and IVO, neoplastic-other); V, suspicious for malignancy; and VI, malignant. The IVB category mostly comprises serous cystadenoma (SCA) and lymphangioma, whereas IVO is a heterogeneous category, including intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) of any grade, pancreatic neuroendocrine tumors (PanNETs), and solid pseudopapillary neoplasms (SPNs), with malignant potential [9, 14]. The PSC reporting system provided a guide to the morphological criteria and risk stratification of each of the cytologic reporting categories incorporating radiologic, biochemical, and ancillary technique findings, and facilitated the communication between cytopathologists and clinicians [8].

Diagnostic performance of pancreatic cytology using the PSC reporting system has been published by many authors since 2014 [2, 3, 15–22]. The neoplastic category included both benign and malignant lesions and yielded an overall risk of malignancy (ROM) of 0–31% despite some lesions being high-risk warranting surgical resection. Hoda et al. [2] reported on ROM for 2 subcategories of neoplastic-other (category IV: other): low-grade atypia (LGA) versus high-grade atypia (HGA). The reported ROM for all grades of category IV: other was 30%, but the ROM increased to 90% when classified into category IV: other with HGA [2]. Neoplastic: benign (ROM, 0%), neoplastic: other (ROM, 0–34%), and neoplastic: other with HGA (ROM 64–100%) have been reported in the literature [8]. Pitman et al. [23, 24] described HGA in IPMN and MCN as background necrosis, chromatin pattern changes, increased nuclear/cytoplasmic (N/C) ratio, small cell size compared to an enterocyte, and nuclear membrane irregularities.

The World Health Organization (WHO) has been preparing an updated reporting system for pancreato-biliary cytopathology that follows the WHO Classification of Tumours of the Pancreas published in 2019 [25]. In alignment with the recent WHO Classification of the Digestive System Tumors, PanNET and SPN are in the “malignant” category, and SCA and lymphangioma are now classified as “benign/negative for malignancy” [23, 25]. “Pancreatic neoplasm-low risk/grade (PaN-Low) and pancreatic neoplasm-high risk/grade” (PaN-High) categories have been created instead of “neoplastic: other” category. IPMN or MCN with low-to-intermediate- and high-grade dysplasia are in this category, respectively [23].

Changes to the PSC system and the proposed WHO System defined by Hoda et al. [23] with examples of diagnostic entities within each category are listed in Table 1. This study aimed to evaluate and compare the ROM of PSC and WHO reporting system categories in our institution.

**Materials and Methods**

All the performed procedures in the current study were approved by the Institutional Research Ethics Board following the 1964 Helsinki Declaration and its later amendments. All patients who underwent EUS-FNA for a pancreatic lesion at the Gazi University Faculty of Medicine Hospital from January 1, 2010, to December 31, 2021, were identified from electronic medical records. Clinical data, including location (head, body, and tail), nature of the lesion (cystic, solid, or both cystic and solid), patients’ age and gender, histopathologic diagnosis, or clinical follow-up information were collected from the pathology reports and/or radiologic imaging reports. Radiologic (computed tomography, magnetic resonance imaging, EUS, and PET) findings, tumor markers (CEA, Ca19-9, and Ca72-4), and amylase levels in peripheral blood, as well as CEA and amylase levels of cystic lesions, were collected. Patients without any surgical or clinical follow-up were excluded from this study.

**Cytologic Evaluation**

Slides of pancreatic EUS-FNA cases from the Gazi University Faculty of Medicine Department of Pathology Archive were re-
The lesion diagnoses were retrospectively classified using both the PSC system and the proposed WHO system.

Direct smears, cytospin preparations, and cell blocks were prepared from FNA samples. Rapid on-site evaluation (ROSE) was performed for a minority of cases. Cell blocks were prepared during the ROSE. Air-dried direct smears were stained by Diff Quick, whereas ethyl alcohol fixed smears by hematoxylin and eosin or Papanicolaou stains, cytospin preparations with Papanicolaou stain, and cell blocks with hematoxylin and eosin. None of the

| Table 1. Diagnostic categories of the PSC system for reporting pancreaticobiliary cytology and proposed diagnostic categories of the WHO international system for reporting pancreaticobiliary cytopathology |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| PSC reporting system categories | Examples of diagnostic entities | WHO system for reporting pancreaticobiliary cytology | Examples of diagnostic entities |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| I. Nondiagnostic                 | Gastrointestinal contamination  | I. Insufficient/inadequate/ nondiagnostic | No proposed changes |
|                                  | Acellular aspirate with no evidence of a mucinous etiology |                                |                                |
|                                  | Benign pancreatic parenchyma, while a well-defined mass is identified on imaging |                                |                                |
| II. Negative for malignancy     | Acute pancreatitis               | II. Negative for malignancy     |                                |
|                                  | Autoimmune pancreatitis          |                                |                                |
|                                  | Benign pancreatic parenchyma, while there is no well-identified mass on imaging |                                |                                |
|                                  | Chronic pancreatitis             |                                |                                |
|                                  | Ectopic spleen                   |                                |                                |
|                                  | Lymphoepithelial cyst            |                                |                                |
|                                  | Pseudocyst                       |                                |                                |
| III. Atypical                   | Atypical ductal cells obscured by artifact, not consistent with normal or reactive changes and not sufficient to classify as a neoplasm or suspicious for high-grade malignancy | III. Atypical                   | No proposed changes |
| IV. Neoplastic: benign          | Lymphangioma                     | IV. PaN-Low                     | IPMN with low-to-intermediate-grade dysplasia |
|                                  | SCA                              |                                | MCN with low-to-intermediate-grade dysplasia |
| IV. Neoplastic: other           | IPMN (of any grade)              | V. PaN-High                     | IPMN with high-grade dysplasia |
|                                  | MCN (of any grade)               |                                | MCN with high-grade dysplasia |
|                                  | Neuroendocrine tumor, well-differentiated (of any grade) |                                |                                |
|                                  | SPN                              |                                |                                |
| V. Suspicious for malignancy   | Rare markedly atypical epithelial cells, insufficient in quality for a positive or malignant diagnosis | VI. Suspicious for malignancy | No proposed changes |
| VI. Positive (for malignancy)  | Ductal adenocarcinoma            | VII. Positive (for malignancy)  | Ductal adenocarcinoma |
|                                  | Acinar cell carcinoma            |                                | Acinar cell carcinoma |
|                                  | Cholangiocarcinoma               |                                | Cholangiocarcinoma |
|                                  | NEC, poorly differentiated       |                                | NEC, poorly differentiated |
|                                  | Pancreatoblastoma                |                                | Neuroendocrine tumor (of any grade) |
|                                  | Metastatic malignancy            |                                | SPN                                |
|                                  | Lymphoma                         |                                | Pancreatoblastoma |
|                                  |                                  |                                | Metastatic malignancy |

Italic and bold means that these tumors are removed from the diagnostic category (changes done in PSC reporting system compared to the proposed WHO reporting system). Bold means that tumors have new diagnostic categories in the proposed WHO reporting system.
cases had molecular analysis for KRAS or GNAS. Cytologic diagnoses were reclassified under the PSC reporting system and the proposed WHO system.

Histopathologic diagnosis or clinical follow-up of patients were searched from the Gazi University Faculty of Medicine Hospital’s Database Program. Adenocarcinoma, adenosquamous carcinoma, metastatic tumors, neuroendocrine carcinoma (NEC), and lymphoma were classified as malignant (true-positive) cytology according to the original PSC reporting system. For the reclassification under the WHO system, NETs of any grade and SPNs were also classified as malignant (true-positive) cytology. Malignant cytologic diagnoses with malignant imaging and/or clinical follow-up features (high serum CEA, CA-19.9 levels, chemotherapy, and radiotherapy) or metastasis were reclassified as malignant (true-positive) even if they did not have histological diagnosis. Benign cytological findings were accepted as true-negative cases if they had benign histology or clinical follow-up with no evidence of metastasis or malignancy. SCA and lymphangioma cases were classified as neoplastic: benign, according to the PSC system, whereas reclassified as negative for malignancy using the proposed WHO system.

Statistical Analyses

The absolute and relative ROM for each diagnostic category was determined as explained in the literature before [23]. p values for relative risks were assessed using Fisher’s exact test. Statistical significance was established at $p = 0.05$. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for various groups of diagnostic categories that are considered positive in both reporting systems as follows: (1) atypical, neoplastic: other with HGA (PaN-High), suspicious, and positive; (2) neoplastic: other with HGA (PaN-High), suspicious, and positive.

Results

Study Cohort

Four hundred and twenty pancreatic EUS-FNA samples from 410 patients were reviewed and reclassified. Of these patients, 225 (55%) were male and 185 (45%) were female with a median age of 58 years and a mean age of 57.1 years (range 12–87 years). Imaging reports of 311 lesions were obtained from our database, of these, 136 (44%) were solid, 105 (34%) were cystic, 45 (14%) were solid and cystic, and 25 (8%) had no visible mass. The lesions were most commonly located in the head of the pancreas ($n = 143$; 46%). Histologic sample was available in 144 (34%) lesions (34 cell blocks and 110 surgical specimens).

Table 2. Comparison and correlation of diagnostic categories of the PSC system for reporting pancreaticobiliary cytology and proposed diagnostic categories of the WHO international system for reporting pancreaticobiliary cytopathology with clinical follow-up and histopathological diagnosis

| Diagnostic categories under WHO system | Histopathologic/clinical follow-up |
|---------------------------------------|-----------------------------------|
|                                       | benign, $n$ (%) | malignant, $n$ (%) | Total, $N$ (%) |
| I. Nondiagnostic                      | 75 (65)         | 40 (35)           | 115 (27.4)    |
| II. Negative for malignancy          | 88 (99)         | 1 (1)             | 89 (21.2)     |
| III. Atypical                         | 5 (31)          | 11 (69)           | 16 (3.8)      |
| IV. PaN-Low                           | 16 (89)         | 2 (11)            | 18 (4.3)      |
| V. PaN-High                           | 0 (0)           | 5 (100)           | 5 (1.2)       |
| VI. Suspicious for malignancy        | 4 (9)           | 39 (91)           | 43 (10.2)     |
| VII. Positive (for malignancy)       | 0 (0)           | 134 (100)         | 134 (31.9)    |
| Total                                 | 188 (45)        | 232 (55)          | 420 (100)     |

| Diagnostic categories under the PSC system | Benign | Malignant | Total |
|--------------------------------------------|--------|-----------|-------|
| I. Nondiagnostic                           | 76 (66)| 39 (34)   | 115 (27.4) |
| II. Negative for malignancy                | 84 (99)| 1 (1)     | 85 (20.2)  |
| III. Atypical                              | 8 (50) | 8 (50)    | 16 (3.8)   |
| IV. Neoplastic: benign                     | 4 (100)| 0 (0)     | 4 (1)      |
| IV. Neoplastic: other                      | 38 (84)| 7 (16)    | 45 (10.7)  |
| With LGA                                   | 38 (95)| 2 (5)     | 40 (89)    |
| With HGA                                   | 0 (0)  | 5 (100)   | 5 (11)     |
| V. Suspicious for malignancy               | 5 (12)| 38 (88)   | 43 (10.2)  |
| VII. Positive (for malignancy)             | 0 (0)  | 112 (100) | 112 (26.7) |
| Total                                      | 214 (51)| 206 (49) | 420 (100) |

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When classified according to the PSC system, our study cohort composed of 115 (27.4%) insufficient/inadequate/nondiagnostic, 85 (20.2%) “negative for malignancy,” 16 (3.8%) “atypical,” 45 (10.7%) “neoplastic: benign,” 43 (10.2%) “suspicious for malignancy,” and 112 (26.7%) “positive or malignant” cases. The application of the proposed WHO criteria yielded 115 (27.4%) “insufficient/inadequate/nondiagnostic,” 89 (21.2%) benign/negative for malignancy, 16 (3.8%) atypical, 18 (4.3%) PaN-Low, 5 (1.2%) PaN-High, 43 (10.2%) suspicious for malignancy, and 134 (31.9%) “malignant” cases. Low-grade NETs ($n = 15$) and SPNs ($n = 7$) were reclassified as malignant under the new proposed WHO reporting system, resulting in an increase in malignant cases. Neoplastic mucinous cysts with low-to-intermediate-grade cytologic atypia ($n = 18$) and high-grade cytologic atypia ($n = 5$) were also in the “neoplastic: other” category. SCA ($n = 3$) and lymphangioma ($n = 1$) which were in “neoplastic: benign” category were reclassified as “negative for malignancy” category under the proposed WHO reporting system. Categories of the two reporting systems with their histologic or clinical follow-up results are summarized in Table 2. Diagnostic classification under both the PSC and WHO systems is summarized in Table 3.

### Table 3. Comparison of diagnostic categories of 420 EUS-FNA samples under the diagnostic categories of the proposed WHO international system for reporting pancreaticobiliary cytopathology and the PSC system for reporting pancreaticobiliary cytology

| The PSC system for reporting pancreaticobiliary cytology | The WHO international reporting system for pancreaticobiliary cytopathology |
|--------------------------------------------------------|--------------------------------------------------------------------------|
| insufficient/inadequate/nondiagnostic, n               | insufficient/inadequate/nondiagnostic, n                                  |
| benign/negative for malignancy, n                      | benign/negative for malignancy, n                                         |
| atypical, n                                            | atypical, n                                                               |
| PaN-Low, n                                             | PaN-Low, n                                                               |
| PaN-High, n                                            | PaN-High, n                                                               |
| suspicious for malignancy, n                           | suspicious for malignancy, n                                             |
| positive or malignant, n                               | positive or malignant, n                                                 |
| total, n (%)                                           | total, n (%)                                                             |
| Nondiagnostic                                          | 115 (27.4)                                                               |
| Negative for malignancy                                | 0                                                                         |
| Atypical                                               | 0                                                                         |
| Neoplastic: benign                                     | 0                                                                         |
| Neoplastic: other                                      | 0                                                                         |
| With LGA                                               | 0                                                                         |
| With HGA                                               | 0                                                                         |
| Suspicious for malignancy                              | 0                                                                         |
| Positive or malignant                                  | 0                                                                         |
| Total, N (%)                                           | 115 (27.4)                                                               |

**Nondiagnostic Cases**

Cytology samples with gastrointestinal contamination only, acellular aspirate of a cyst without evidence of mucinous etiology, and benign acinar and ductal epithelium observed in the aspiration material from a clearly defined solid or cystic mass lesion, as well as preparing or obscuring artifacts that preclude cellular sample evaluations were defined as nondiagnostic. Of the 420 cases, 115 (27.4%) were nondiagnostic, of which 75 (65%) were benign lesions, whereas 40 (35%) were malignant according to the WHO reporting system. One case, which was diagnosed as insulinoma, was accepted as nonmalignant using the original PSC reporting system.

**Negative for Malignancy**

Using the WHO reporting system, 89 (21.2%) cases were reported as negative (for malignancy)/benign, whereas 85 (20.2%) were under the PSC reporting system. Four cases (1 lymphangioma and 3 SCAs), which were classified as neoplastic: benign under the PSC reporting system, were included in the “negative for malignancy” category under the WHO reporting system. Only one case was malignant upon follow-up, with a ROM of 1% in this group, which had cytology rich in neutrophils and was reported as “probably acute pancreatitis” with recommendation to correlate with radiologic, serologic (serum CEA and amylase levels), and clinical findings. This case was diagnosed as ductal adenocarcinoma on histopathology. The final diagnosis for this category was as follows: forty-two (47%) of the 89 cases were chronic pancreatitis, 4 acute pancreatitis, 2 pseudocysts, 2 granulomatous inflammation, 1 ectopic spleen, 1 autoimmune pancreatitis, 1 intestinal duplication cyst, and 4 nonspecific histopathologic findings, whereas 27 cases were benign upon clinical follow-up.
Atypical
Atypical ductal cells that are obscured by artifact, not consistent with normal or reactive changes, and insufficient to be classified as a neoplasm or suspicious for high-grade malignancy were in this category. Sixteen (3.8%) cases were in this group, and ROM under the WHO reporting system was 69%, whereas 50% under the PSC reporting system. The final diagnosis for this category was as follows: six cases were ductal adenocarcinomas, 2 SPNs, 1 NET, 2 malignant upon follow-up, 2 chronic pancreatitis, and 3 benign upon clinical follow-up.

Pancreatic Neoplasia-Low/Intermediate-Grade Atypia/PaN-Low
IPMN with low-to-intermediate-grade dysplasia and MCN with low-to-intermediate-grade dysplasia are in this category. Low-grade neoplasms have mild to moderate atypia, well-oriented nuclei without pseudostratification, simple papillae, and rare mitoses [25] “(shown in Fig. 1a, b).” Eighteen cases were included in this category, wherein 2 (11%) cases were histopathologically diagnosed as adenocarcinoma. One case was reported as mucinous neoplasm with LGA, and another case was reported as mucinous neoplasm with moderate atypia in the cytology. They were both histopathologically diagnosed as adenocarcinoma. The remaining 16 cases were benign in the follow-up, wherein 4 were MCNs, 11 were IPMNs, and 1 was intraductal tubulopapillary neoplasm.

Pancreatic Neoplasia-HGA/PaN-High
Five cases were in this category as defined by Pitman et al. [23, 24] and the ROM was 100% when using both the WHO and PSC reporting systems. In our 5 cases, thick mucin in the background, papillary structures lined by atypical epithelial cells with high N/C ratio, nuclear membrane irregularities, and chromatin pattern changes were observed. One case had background necrosis. All cases were consistent with IPMN with high-grade dysplasia on cytology and all were ductal adenocarcinomas histopathologically “(shown in Fig. 2a, b).”

Suspicious for Malignancy
This category included 43 of our cases, of which 39 (91%) were malignant under the WHO reporting system. Thirty-one (76%) of the 39 cases were ductal adenocarcinomas, 1 was adenosquamous carcinoma, 1 was undifferentiated carcinoma, 2 were NECs, 1 was mixed neuroendocrine-non-neuroendocrine neoplasm, 1 was NET, and 2 were malignant upon clinical follow-up. One case that was consistent with NET was classified in the non-malignant group according to the PSC reporting system. Thus, the ROM was 88% under the PSC reporting system.

Fig. 1. a IPMN-LGA cytology: thick mucin in the background consistent with a mucinous neoplasm, and an epithelial group with LGA (Diff-Quick ×400). b IPMN-LGA cytology: simple papillary structures lined by well-oriented epithelial cells with mild-moderate nuclear pleomorphism and smooth nuclear contours; consistent with LGA (PAP ×200).

Fig. 2. a IPMN-HGA cytology: complex papillary structures lined by epithelial cells with high nuclear-to-cytoplasmic ratio, nuclear membrane irregularities, and abnormal chromatin pattern (PAP ×400). b IPMN-HGA cytology: high-grade atypical epithelial cells with necrosis in the background (PAP ×400).
Four cases (9%) were benign in the follow-up (three chronic pancreatitis on histology and one benign without any evidence of malignancy). One of the benign cases had neuroendocrine cell proliferation on cytology and was reported as “NET can’t be ruled out.” This case was consistent with chronic pancreatitis on histology. Two cases had atypical ductal epithelial cells and background necrosis, which was reported as suspicious for malignancy with a comment that low-grade ductal adenocarcinoma or a reactive inflammatory process cannot be distinguished. A clinical, radiologic, and serologic correlation was recommended. Both of these cases were consistent with chronic pancreatitis on histology. Another case had discohesive round cells with a high N/C ratio in the background. No cell block was available. This was called “suspicious for malignancy” with a comment that neuroendocrine cell proliferation or a non-Hodgkin lymphoma cannot be distinguished. Thus, repeat FNA by ROSE was recommended. This case had no signs of malignancy upon clinical follow-up, with EUS images and laboratory findings consistent with chronic pancreatitis.

**Positive for Malignancy**

Under the WHO reporting system, 134 (31.9%) cases were in the malignant group, whereas 112 (26.7%) were under the PSC reporting system. ROM was 100% for both reporting systems. Twenty-two cases, which were diagnosed as neoplasia: other (NET or SPN), were malignant according to the WHO reporting system “(shown in Fig. 3–4).” Follow-up diagnoses for this category were as follows: 100 (75%) ductal adenocarcinomas, 5 NETs, 7 SPNs, 5 metastatic tumors (1 small-cell lung carcinoma, 1 clear cell renal cell carcinoma, 1 leiomyosarcoma, 1 ovarian carcinoma, 1 hepatocellular carcinoma), 2 acinic cell carcinomas, 2 diffuse large B-cell lymphomas, 1 anaplastic malignant tumor with epithelioid morphology.

**Follow-Up**

The clinical follow-up with a median time of 58 months was available in 276 (66%) cases. The minimum follow-up time was 6 months. Of the 232 (55%) malignant cases, 157 (67.7%) ductal adenocarcinomas, 18 NETs (low-to-moderate grade), 9 SPNs, 6 metastatic tumors (2 small-cell lung carcinomas, 1 clear cell renal cell carcinoma, 1 leiomyosarcoma, 1 ovarian carcinoma, and 1 hepatocellular carcinoma), 3 lymphomas (2 diffuse large B-cell lymphomas and 1 extranodal marginal zone B-lymphoma), 2 adenosquamous carcinomas, 2 acinic cell carcinomas, 2 mixed neuroendocrine-non-neuroendocrine plasmas, 2 NECs, 1 extragastrointestinal stromal tumor-high risk, 1 undifferentiated carcinoma, and 1 anaplastic tumor with epithelioid morphology were determined.
The cytology and imaging of 28 patients were malignant without a specific diagnosis. Of the 188 benign cases, 70 (37.2%) chronic pancreatitis, 14 IPMNs with LGA, 8 MCAs with LGA, 7 SCAs, 4 acute pancreatitis, 4 granulomatous inflammation, 2 intestinal duplication cysts, 2 cyst hydatid, 1 autoimmune pancreatitis, 1 lymphangio, 1 ectopic spleen, and 1 ischemic pancreas were diagnosed, and the remaining 73 cases were benign in the clinical follow-up.

The absolute ROM for each diagnostic category of the proposed WHO system was as follows: 35% for insufficient/inadequate/nondiagnostic category, 1.0% for benign/negative for malignancy, 69.0% for atypical, 11% for PaN-Low, 100% for PaN-High, 91% for suspicious for malignancy, and 100% for malignant. The absolute ROM for the same cohort with the diagnostic categories of the PSC system was as follows: 34% for the nondiagnostic category, 1.0% for negative (for malignancy), 50.0% for atypical, 0.0% for neoplastic: benign, 16% for neoplastic: other, 5% for neoplastic: other with LGA, 100% for neoplastic: other with HGA, 88% for suspicious (for malignancy), and 100% for positive or malignant. The comparison of the absolute and relative ROM of the diagnostic categories of the PSC and WHO reporting systems and the categories with statistically significant differences in the ROM from that of the negative category are presented in Table 4.

The sensitivity, specificity, PPV, and NPV were calculated for various groups of diagnostic categories of both reporting systems considered positive as (1) atypical, neoplastic: other with HGA/PaN-High, suspicious, and positive and (2) neoplastic: other with epithelial HGA/PaN-High, suspicious, and positive. The sensitivity, specificity, and NPV were higher when the “atypical,” “neoplastic: other with epithelial HGA/PaN-High,” “suspicious,” and “positive” was considered positive. The proposed WHO reporting system had slightly higher results than the PSC system. The results are summarized in Table 5.

**Discussion**

The PSC reporting system was developed to improve the communication between cytopathologists and clinicians, and standardize the algorithmic approach for patient management by providing risk stratification and supporting a multimodal approach with cytomorphologic, biochemical, radiologic, and molecular findings [9, 14]. Nondiagnostic and atypical interpretations have been reduced by this standardized system [16, 26].

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**Table 4.** Comparison of absolute risk and relative risk of malignancy of diagnostic categories of the proposed WHO international system for reporting pancreaticobiliary cytopathology and the PSC system for reporting pancreaticobiliary cytology

| Reporting system | Diagnostic category                        | Absolute ROM % | Relative risk % | p (relative to benign category) |
|------------------|--------------------------------------------|----------------|-----------------|--------------------------------|
| WHO              | I. Insufficient, inadequate, nondiagnostic | 35             | 35              | <0.001<sup>a</sup>             |
|                  | II. Benign/negative for malignancy         | 1              | 1               | –                              |
|                  | III. Atypical                              | 69             | 69              | <0.001<sup>a</sup>             |
|                  | IV. PaN-Low                                | 11             | 11              | 0.07                           |
|                  | V. PaN-High                                | 100            | 100             | <0.001<sup>a</sup>             |
|                  | VI. Suspicious for malignancy              | 91             | 91              | <0.001<sup>a</sup>             |
|                  | VII. Positive for malignancy               | 100            | 100             | <0.001<sup>a</sup>             |
| PSC              | I. Nondiagnostic                           | 34             | 34              | <0.001<sup>a</sup>             |
|                  | II. Negative for malignancy                | 1              | 1               | –                              |
|                  | III. Atypical                              | 50             | 50              | <0.001<sup>a</sup>             |
|                  | IV. Neoplastic: benign                     | 0              | 0               | 1                              |
|                  | IV. Neoplastic: other                      | 16             | 16              | 0.003<sup>a</sup>             |
|                  | Neop: other with LGA                       | 5              | 5               | 0.24                           |
|                  | Neop: other with HGA                       | 100            | 100             | <0.001<sup>a</sup>             |
|                  | V. Suspicious for malignancy               | 88             | 88              | <0.001<sup>a</sup>             |
|                  | VI. Positive for malignancy                | 100            | 100             | <0.001<sup>a</sup>             |

<sup>a</sup>Denotes a statistically significant p value <0.05 by Fisher’s exact test.
nostic performance of pancreatic cytology with the PSC reporting system has been published by many authors since 2014 [2, 3, 15–22]. Recently, a systematic review has been published by Nikas et al. [8], wherein ROM of all PSC system categories was reported as follows: I, nondiagnostic (ROM, 8–57%); II, negative (ROM, 0–40%); III, atypical (ROM, 28–100%); IV, neoplastic (overall ROM, 0–31%) IVB, neoplastic-benign (ROM, 0%); IVO, neoplastic-other (ROM, 0–34%); IVO with HGA (ROM, 64–100%); V, suspicious for malignancy (ROM, 80–100%); and IV, malignant (ROM, 97–100%) [8].

Hoda et al. [23] have reported the absolute and relative ROM of 334 EUS-FNA samples under both the PSC and WHO international reporting systems. The ROM under the WHO reporting system was as follows: I, nondiagnostic (ROM, 7.7%); II, negative (ROM, 1%); III, atypical (ROM, 28%); IV, PaN-Low (ROM, 4.8%); V, PaN-High (ROM, 60%); VI, suspicious for malignancy (ROM, 100%); and VII, malignant (ROM, 97–100%) whereas ROM under the PSC system was different from the proposed WHO reporting system in only IV, neoplastic: other category (ROM 30.3%) and neoplastic: benign category (ROM 0%).

In our study, the ROM under the WHO reporting system was as follows: I, nondiagnostic (ROM, 34%); II, negative (ROM, 1%); III, atypical (ROM, 50%); IV, neoplastic (overall ROM, 14.3%); IVB, neoplastic-benign (ROM, 0%); IVO, neoplastic-other (ROM, 16%); IVO with LGA (ROM, 5%); IVO with HGA (ROM, 100%); V, suspicious for malignancy (ROM, 88%); and IV, malignant (ROM, 100%). Our findings were similar to the literature [8]. Additionally, the ROM under the WHO reporting system was as follows: I, nondiagnostic (ROM, 35%); II, negative (ROM, 1%); III, atypical (ROM, 69%); IV, PaN-Low (ROM, 11%); V, PaN-High (ROM, 100%); VI, suspicious for malignancy (ROM, 91%); and VII, malignant (ROM, 100%), similar ROM to Hoda et al. [23], except the “nondiagnostic” and “atypical” categories.

Nondiagnostic category has a ROM of 8–57% in the literature which is concordant with our findings. This underscores the importance of improved collection protocols, e.g., ROSE or implementation of cell blocks to reduce this high rate of non-diagnostic samples. Next-generation “core-type” needles which had apparently contributed to a higher diagnostic yield from solid lesions, with a decrease in the number of suspicious and atypical cases by producing larger tissue fragments can also be used [26–28].

In our study, the ROM of the “atypical” category was 69% and 50% under the WHO and PSC reporting systems, respectively. The “atypical” diagnosis was given in all cases because either the cytological material was hypocellular or only a few tumoral cells did not meet the criteria for “suspicious for malignancy” or “benign.” This difference in ROMs in the “atypical” category is due to the two SPN cases and one NET case in the cohort. In the literature, the “atypical” category has a ROM that ranges between 28% and 100%, in concordance with our results [8]. Specificity and PPV were higher when the “neoplastic: other with epithelial HGA/PaN-High,” “suspicious,” and “positive” was considered positive. The proposed WHO reporting system had slightly higher PPV than the PSC system.

In the original PSC system neoplastic: other category defines a neoplasm that is either premalignant such as IPMN or MCN with any grade of dysplasia using cytological criteria, or a low-grade malignant neoplasm such as well-differentiated PanNETs or SPNs. This category

| Diagnostic categories considered positive (PSC) | Sensitivity | Specificity | PPV | NPV |
|-----------------------------------------------|-------------|-------------|-----|-----|
| Atypical, neoplastic: other with HGA, suspicious, and positive | 97.6 | 91.3 | 92.6 | 97.7 |
| Neoplastic: other with HGA, suspicious, and positive | 92.8 | 97.1 | 96.9 | 92.4 |

| Diagnostic categories considered positive (WHO) | Sensitivity | Specificity | PPV | NPV |
|-----------------------------------------------|-------------|-------------|-----|-----|
| Atypical, PaN-High, suspicious, and positive | 98.4 | 92 | 95.5 | 97.2 |
| Neoplastic: PaN-High, suspicious, and positive | 92.7 | 96.5 | 97.8 | 88.6 |

PPV, positive predictive value; NPV, negative predictive value.
represented the most controversial aspect of the PSC reporting system. The rationale for this category related the desire to standardize and correlate the cytological nomenclature with the 2010 WHO terminology classification that maintained the nomenclature for both PanNET and SPN as “neoplasms” rather than carcinomas, and to take into consideration the increasingly conservative management approaches for many of the lesions [29].

The addition of “neoplastic other: low grade” and “neoplastic other: high grade” subcategories to the PSC reporting system significantly contributed to risk stratification in the literature [2, 3, 15–22]. In our study, the ROM for the “neoplastic: other with LGA” group was 5% and was 100% in the “neoplastic: other with HGA” group. The HGA group consisted of 5 cases, of which all showed abnormal epithelial cells with high N/C ratio, membrane irregularity, and irregular chromatin pattern covering the surface of papillary structures in a background of thick mucin, consistent with IPMN-HGA. One of the 5 cases contained necrotic debris. In our study, the ROM of neoplastic: other with HGA and Pan-N-High category was statistically different from the “negative for malignancy” category (p < 0.001), whereas the neoplastic other with LGA and Pan-N-Low categories were not statistically different from the “negative for malignancy” category (p = 0.07 and p = 0.24), respectively. These results are similar to the only report for the ROM of the proposed WHO international reporting system [23].

Our study is limited by its retrospective design with histopathologic follow-up in only 34% of the cases and a low number of PAN-High cases. However, it provides useful information about the ROM of the proposed WHO international reporting system categories in a large number of patient cohorts.

This study has revealed that the Pan-N-High group could at least be included in the “suspicious for malignancy” category due to its high ROM (100%). In our study, a separate group for these cases seems to be unnecessary, since these patients already need surgery for management because of risk of having invasive components [29].

In conclusion, the inclusion of SPN and NET diagnoses in the “positive for malignancy” group under the proposed WHO reporting system is a justifiable decision as those tumors have a malignant behavior and have the potential to metastasize despite their low nuclear grade. Additionally, a separate “neoplastic: benign” category for the SCA and lymphangioma cases is unnecessary, since those cases can be radiologically followed-up. Creating Pan-N-High and Pan-N-Low categories lends valuable information about the grade of atypia and helps decide the triage of management. Therefore, the proposed WHO reporting system for pancreaticobiliary cytology has advantages in terms of creating a common language between cytopathologists and clinicians regarding risk stratification improvement and case management.

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Statement of Ethics

This study protocol was reviewed and approved by the Gazi University Clinical Research Ethics Committee, approval number (140), date (February 21, 2022). Since it was a retrospective research on archival material, informed consent was not required by decision of the Gazi University Clinical Research Ethics Committee.

Conflict of Interest Statement

We do not have a financial, commercial, legal, or professional relationship with other organizations, or with the people working with them, that could influence our research.

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Author Contributions

Pınar Uyar Gocun: conceptualization, methodology, project administration, data curation, investigation, re-evaluation of cytologic and histopathologic slides, supervision, and writing – original draft and editing. Berkay Simsek: data curation, methodology, re-evaluation of cytologic and histopathologic slides, taking photographs, and editing. Özgür Ekinci: data curation, methodology, re-evaluation of histopathologic slides, and editing. Nergis Ekmen, Mehmet Arhan, Tarkan Krakan, and Mehmet Ibis: data curation and editing. Mehmet Cindoruk: data curation, investigation, and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.
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