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Asian Archives of Pathology (AAP) is an open access, peer-reviewed journal. The journal was first published in 2002 under the Thai name "วารสารราชวิทยาลัยพยาธิแพทย์แห่งประเทศไทย" and English name "Journal of the Royal College of Pathologists of Thailand". The journal is a publication for workers in all disciplines of pathology and forensic medicine. In the first 3 years (volumes), the journal was published every 4 months. Until 2005, the journal has changed its name to be "Asian Archives of Pathology: The Official Journal of the Royal College of Pathologists of Thailand", published quarterly to expand the collaboration among people in the fields of pathology and forensic medicine in the Asia-Pacific regions and the Western countries.

The full articles of the journal are appeared in either Thai or English. However, the abstracts of all Thai articles are published in both Thai and English languages. The journal features letters to the editor, original articles, review articles, case reports, case illustrations, and technical notes. Diagnostic and research areas covered consist of (1) **Anatomical Pathology** (including cellular pathology, cytopathology, haematopathology, histopathology, immunopathology, and surgical pathology); (2) **Clinical Pathology (Laboratory Medicine)** [including blood banking and transfusion medicine, clinical chemistry (chemical pathology or clinical biochemistry), clinical immunology, clinical microbiology, clinical toxicology, cytogenetics, parasitology, and point-of-care testing]; (3) **Forensic Medicine (Legal Medicine or Medical Jurisprudence)** (including forensic science and forensic pathology); (4) **Molecular Medicine** (including molecular genetics, molecular oncology, and molecular pathology); (5) **Pathobiology**; and (6) **Pathophysiology**.

All issues of our journal have been printed in hard copy since the beginning. Around the late 2014, we developed our website (www.asianarchpath.com) in order to increase our visibility. We would like to acknowledge that our journal has been sponsored by the Royal College of Pathologists of Thailand. We have the policy to disseminate the verified scientific knowledge to the public on a non-profit basis. Hence, we have not charged the authors whose manuscripts have been submitted or accepted for publication in our journal.

On the other hand, if any authors request a printed copy of the journal issue containing the articles, each of the copied journals costs 450 bahts for Thai authors and 30 United States dollars (USD) for international authors.

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CONTENTS

ORIGINAL ARTICLE

Characteristics of BRCA-carrier patients attending for risk reducing salpingo-oophorectomy (RRSO) at King Chulalongkorn Memorial Hospital (KCMH)

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Abstract

Background: KCMH started perform RRSO in patients with BRCA1 and BRCA2 mutation in 2017. Clinical and pathological information are necessary for optimal care.

Objectives: The primary objective aimed to evaluate characteristics of BRCA1 and BRCA2 mutation patients who were assigned to perform RRSO. The secondary objective was to identify the proportion of occult malignancies in patients who were assigned to perform RRSO.
Materials and methods: A retrospective study was performed in patients who carried BRCA1 or BRCA2 gene mutations who were assigned to perform RRSO in KCMH. General characteristics and pathologic specimens were reviewed.
Results: There were 18 cases who were assigned to perform RRSO. The BRCA1 carrier patients were older than BRCA2 carrier (51.5 vs 47.0 years). Preoperative pelvic ultrasound revealed 2 patients with suspicious pelvic masses which was later confirmed to be malignancy. No occult fallopian tube cancer or precursor lesions was found after SEE-FIM protocol.
Conclusion: We provide informative data from our institution's recently opened genetic services. No occult fallopian tube cancer or precursors lesions was found in SEE-FIM protocol after RRSO. In premenopausal women, menopausal symptoms may develop after RRSO. Further study with larger sample size is required.

Keywords: BRCA, hereditary, HBOC, RRSO, SEE-FIM

Introduction

Breast and ovarian cancers are among the most devastating cancers for women. Breast cancer is the most prevalent cancer and ovarian cancer is the seventh leading cancer related cause of death in women worldwide [(1)]. Hereditary cancer is responsible for 5-25% of breast or ovarian cancer. Heredity breast and ovarian cancer (HBOC) caused by pathogenic variants in BRCA1 or BRCA2. The majority of heredity cancer in breast and ovarian cancer patients accounts for more than 50% of all genetic predisposition in families. BRCA1 and BRCA2 are tumor suppressor genes involving in homologous recombination DNA repair [(2,3)]. Individuals

who carry pathogenic variants in BRCA 1 or BRCA2 have a significantly increased risk for breast and ovarian cancer. By the age of 70, women with BRCA1 and BRCA2 pathogenic variants have a 35-45% and 15-18% accumulative risk of ovarian cancer, respectively [(4)].

Risk reducing strategies are proposed in several options. The mainstay of ovarian cancer risk reduction in BRCA carrier patients is risk-reducing salpingo-oophorectomy surgery (RRSO). RRSO is recommended for both BRCA1 and BRCA2 mutation patients. For BRCA1 mutation, RRSO should be performed at 35-40 years old. For BRCA2, 40-45 years old is the recommended age to perform RRSO [(5)]. Previous studies showed that RRSO decreases the risk of ovarian cancer in BRCA carrier patients by 80% [(4,6)]. Moreover, RRSO can decrease ovarian cancer specific mortality and all causes of mortality at the age of 70 years. However, the magnitude of protection varies by mutation type. The reduction of cancer risk seems to be stronger in BRCA1 mutation patients than in BRCA2 mutation patients. RRSO also reduces the risk of breast cancer up to 50% [(7)].

On the other hand, RRSO causes early menopause and several consequences. Significantly worsening hot flashes and night sweats can occur in the first year after surgery, especially in premenopausal women. Moreover, the risk of dyslipidemia, coronary heart disease, and cognitive dysfunction might also increase [(8)]. Discussion of the risks and benefits of this risk reducing procedure should be offered at the time that genetic testing is considered. From a previous study of RRSO cases, occult malignancies can be identified at the time of RRSO. An incidence of occult malignancies varies from zero up to as high as 17% [(9)]. Complete pathological examination of these groups of patients might be an issue in low prevalence series, whereas the proportion of the older age group can overestimate the risk of identifying occult malignancies in the study. The major risks for higher incidence of occult malignancies are the increasing age at RRSO and mutation type [(10)]. Age of more than 45 years increases risk of occult malignancy at time of RRSO. The incidence of occult malignancy in BRCA1 is higher than BRCA2 mutation patients at the same age of RRSO [(10)].

At the King Chulalongkorn Memorial Hospital (KCMH), we started perform RRSO in patients with BRCA1 and BRCA2 mutation in 2017. This study was conducted to collect data from BRCA1 and BRCA2 mutation patients who were assigned for ovarian cancer risk reduction surgery at KCMH. Primary objective was to evaluate the characteristics of BRCA1 and BRCA2 mutation patients who were assigned to perform RRSO in our institution. The secondary objective was to identify the proportion of occult malignancies in patients who were assigned to perform RRSO.

Materials and Methods

After approval form Ethics Committee was achieved, a retrospective study was performed. The data were retrieved from the electronic medical database of the hospital. Inclusion criteria were patients who carried pathogenic or likely pathogenic variants in BRCA1

or BRCA2 and were assigned to perform RRSO in KCMH during 1 January 2017 to 31 December 2020. Patients with missing significant data and whose pathologic slides or paraffin blocks were unable to be reviewed were excluded.

From the patient registration data from the Excellence Center for Medical Genetics, every patient who carried pathogenic or likely pathogenic variants of BRCA 1 or BRCA 2 during January 2017 to December 2020 were collected. All patients underwent multiple gene panel testing with next-generation sequencing (CLIA and CAP certified laboratory) that was commercially available. After pathologic BRCA 1 or 2 mutation were confirmed, the patients were sent to gynecologic oncologist. Counselling about pros and cons of risk reducing surgery and the appropriate age to do the operation were performed. The appropriate age for RRSO in BRCA 1 mutation was 35-40 years old and 40-45 years old for BRCA 2 mutation. In case that the patients presented at older than appropriate age, RRSO was perform as soon as possible. For the patients who had co-existing uterine pathology, hysterectomy was offered in the same operation of RRSO. Laboratory examination including CBC, BUN, creatinine, liver function test, CA-125, HE4, and pelvic ultrasound were performed before the operation. In case that any abnormalities were identified, further preoperative consultation or investigation were performed. All fallopian tubes were examined according to the sectioning and extensively examining the fimbria (SEE/FIM) protocol which was the standard protocol for evaluation of RRSO specimen [(11)].

General characteristics of the patients (i.e., age at analysis time, age at diagnosis of BRCA-related conditions and age at RRSO) were collected. Family history, underlying cancer of the patients, type of BRCA mutation, operative data and operative complication, pathologic results and post-operative menopausal symptoms were also collected. Last follow up visit of the patients was also reviewed to evaluate the current status of the patients. Pathologic specimens were all reviewed by a gynecologic pathologist (CA). In the case of any conflicting results between the previous report and current review, slides were sent to a third pathologist for review. At which point, a diagnosis was made by majority rule.

After retrieving the data, statistical analysis was performed. Descriptive data were analyzed and presented as mean, median, interquartile range and percentage. Independent sample t-test and Fisher's exact test were using to compared between groups. All statistical data were analyzed with IBM SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and results are presented in tables.

Results

During January 2017 to December 2020, there were 18 cases of BRCA 1 and BRCA 2 – related patients (12/18 (66.6%) in BRCA1, and 6/18 (33.3%) in BRCA2) who were assigned to performed RRSO had pathological results. Mean age at the procedure was 50.0 years (SD = 10.40). The BRCA1 carrier patients were older than BRCA2 carrier (51.50 VS 47.00 years). Weight,

height and BMI were not different in both groups (*table 1*). Median duration from diagnosis BRCA mutation to RRSO was 80 days. Median duration from diagnosis to RRSO in BRCA 1 and BRCA 2 group were not different (78 days in BRCA 1 and 89 days in BRCA 2, p = .723). Most of the patients in both BACA 1 and BRCA 2 had a history of breast cancer (83.3% both). Moreover, most of them had family history of cancer (83.3%). Seventy-five percent (75%, 9/12) of BRCA1 mutation patients had a family history of breast cancer and 8.3% (1/12) had a family history of both breast and ovarian cancers. About one-third (2/6) of BRCA2 mutation patients had a family history of breast and ovarian cancer. One patient in the BRCA2 mutation group had a family history of both breast and ovarian cancers.

Table 1: Characteristics of *BRCA1* and *BRCA2* gene mutation patients who were assigned to perform RRSO

	BRCA 1 (N=12)	*BRCA 2* (N= 6)	All (N=18)	p value
Age (yr) (mean(SD))	53.0 (10.54)	48.33 (10.01)	51.44 (10.34)	.381
Age at RRSO (yr) (mean(SD))	51.50 (10.79)	47.00 (9.77)	50.00 (10.40)	.403
Weight (kg) (mean(SD))	59.53 (17.36)	59.28 (5.60)	59.4 4(14.29)	.974
Height (cm) (mean(SD))	158.58 (6.97)	159.83 (3.31)	159.00 (5.92)	.686
BMI(kg/cm2) (mean(SD))	23.26 (5.78)	23.20 (2.06)	23.24 (4.79)	.980
Duration from Dx to RRSO (days) (median(IQR))	78 (61-221)	89 (56-262)	80 (61-221)	.723
Follow up duration(months) (median(IQR))	16 (6-18)	11.5 (4-16)	12 (5.5-18)	.319
History of CA breast (n (%))	10 (83.3)	5 (83.3)	15 (83.3)	.730
Family history of CA (n (%))				
No	2 (16.7)	1 (16.7)	3 (16.7)	.730
Breast	9 (75.0)	2 (33.3)	11 (61.1)	
Ovary	0 (0)	2 (33.3)	2 (11.1)	
Breast + Ovary	1 (8.3)	1 (16.7)	2 (11.1)	
Menopausal symptoms (n(%))	1 (8.3)	2 (33.3)	3 (16.7)	.245
Current status (n (%))				
On chemotherapy	2 (16.7)	1 (16.7)	3 (16.7)	.755
Follow up NED	10 (83.3)	6 (100)	16 (88.9)	.431

RRSO: Risk reducing salpingo-oophorectomy, SD: standard deviation, IQR: interquartile range, NED: no existing disease

Two patients were found to have pelvic masses during pelvic ultrasound examination preoperatively which was later confirmed to be malignancy. The first patient was 72 years old. She was diagnosed Breast cancer several years ago. Her younger sister was also diagnosed breast cancer and performed genetic testing. Her sister had BRCA 1 mutation. After that, the patient was called to performed genetic testing and found that she also had BRCA 1 mutation. RRSO was counselling. Her preoperative pelvic ultrasound found mixed echoic pelvic mass 7 cm in diameter. TAH with BSO with surgical staging was performed. The pathologic results showed that high grade serous carcinoma at left fimbria invaded wall of fallopian tube (*figure1*). Uterus, right adnexa, lymph nodes and omentum were negative for malignancy. At time of review (April 2021), she had received the fourth cycle of carboplatin and paclitaxel. She was doing well during the chemotherapy session. The second patient was 57 years old. She had a history of locally advanced stage breast cancer. She had strong family history of breast cancer. She has 2 sisters and 2 siblings diagnosed breast cancer. Genetic testing was performed and BRCA 1 mutation was detected. Gynecologic oncologist was consulted. Her last pelvic examination was several years ago. Her pelvic ultrasound was performed and large pelvic mass was found. The doctor suspected advanced stage ovarian cancer. Therefore, neo-adjuvant chemotherapy was administered. Interval debulking was performed. The final histopathologic and immunohistochemical study revealed that the tumor was moderately

differentiated adenocarcinoma compatible with metastasis invasive ductal carcinoma (*figure 2*). She is currently receiving targeted therapy (Talozoparib) for breast cancer with disease stability.

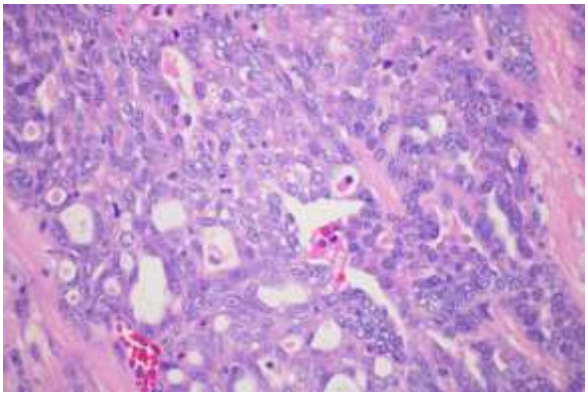

Figure 1: High grade serous carcinoma of the 72-year-old woman with BRCA1 mutation and adnexa mass. The tumor architecture pattern includes solid and hierarchical branching of variably size papillae with slit-like spaces with prominent nuclei and frequent mitotic figures.

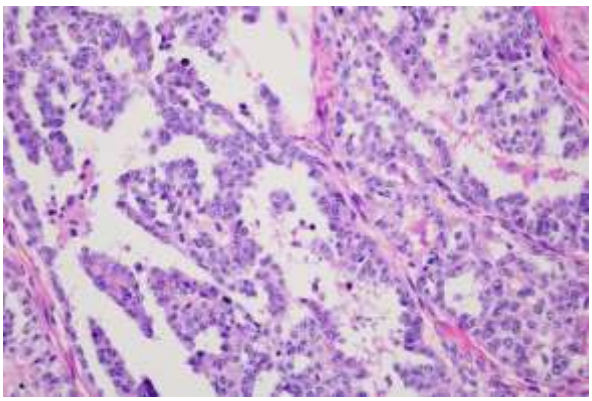

Figure 2: Metastatic breast cancer of the 58 years old women with BRCA1 and pelvic mass. The tumor possesses trabecular and cords pattern with minimal nuclear pleomorphism. Further immunohistochemical study of estrogen and progesterone receptor are reactive.

Therefore, the other 16 patients without suspicious pelvic scan were underwent RRSO. All fallopian tube and ovarian specimens, no precursor lesions of high-grade serous carcinoma, including serous tubal intraepithelial carcinoma (STIC) or occult invasive cancer were found from SEE-FIM protocol.

Post-operation menopausal symptoms were reported in 3 patients (3/18: 16.7%). For the patients who had menopausal symptoms, one of them was 50 years old with BRCA 1 mutation and 2 of them were 41 and 43 years old with BRCA 2 mutation. Hot flashes and night sweats were reported. Those patients were sent to the menopausal clinic and lifestyle modification was advised. No patients received hormonal treatment. Follow up time since

RRSO or operation was 15.73 months in BRCA1 and 11.17 months in BRCA2 mutation patients. All patients in this series were still alive until the reviewing time.

Discussion

BRCA1 and BRCA2 gene mutations are the most common cause of hereditary breast and ovarian cancer. Risk-reducing salpingo-oophorectomy surgery or RRSO is an important risk reduction strategy. RRSO does not only reduce the risk of ovarian cancer, but also reduces risk of other cancers such as breast cancer and peritoneal cancer [(12)]. For patients who still hesitate to perform RRSO, prophylactic salpingectomy with delayed oophorectomy (PSDO) may be an option in those patients who did not complete their family. However, intensive counselling about risks and benefits should be performed.

From 18 patients who were assigned to perform RRSO, 2 of them were detected pelvic mass by pelvic ultrasound. Therefore, the operation was changed to surgical staging for one case and neo-adjuvant chemotherapy followed by interval debulking for another case. Therefore, pelvic ultrasound before the operation can help detecting pelvic mass and guide for the proper management. The other 16 patients were performed RRSO and the specimen was evaluated according to SEE-FIM protocol. No occult malignant was found in these cases. For the 72 years old patient who were diagnosed fallopian tube cancer, her cancer is preventable if RRSO was performed at the appropriate age.

Previous studies showed that incidence of occult cancer varies from 0-17% [(9)]. Our study cannot detect the occult cancer because the number of BRCA 1 and 2 mutations patients in this study are quite small. Therefore, larger cohort is required.

In the aspect of characteristics, mean age at RRSO in BRCA1 and BRCA2 carrier patients in this study was 51.5 years old and 47.0 years old, respectively. While, the recommended age to perform RRSO is 35-40 years for BRCA1 carrier patients and 40-45 years for BRCA2 carrier patients. BRCA2 carrier patients in this study underwent RRSO near the recommendation age but BRCA1 carrier patients was performed RRSO much later than the recommendation age. The overall age at RRSO in this study is considered older than other previous studies. While the patients in long run service setting may perform genetic testing because their relative with a known BRCA1 or BRCA2 mutation, the patients in the latter group are younger than the patients in the former group. Our genetics services started in 2017, which was 3 years ago. The majority of the patients for genetic testing were personal history of two or more types of cancer, a second primary breast cancer or strong family history of cancer. For this reason, the characteristics of the patients in this study maybe different from the previous study.

Menopausal symptoms were reported in a few patients: 3 in 18 patients (16.7%), 1 in BRCA1 cases (50 years old) and 2 BRCA2 cases (41 and 43 years old). It is well established that the menopausal symptoms occur more frequently in premenopausal women than postmenopausal women who underwent oophorectomy. No patient in this study received

postmenopausal hormonal treatment with concerns for risk of breast cancer prognosis and treatment. All patients in this study were still alive at the reviewing time. Three patients are ongoing treatment. Two of them continues to receive chemotherapy for fallopian tube cancer and breast cancer and one patient receives targeted therapy for breast cancer.

This study collected the data since the opening of the genetic counseling and genetic testing service at our institution for three years. This data may be some information for other newly open services. However, this study still has limitations. First, the sample size is quite small. Therefore, occult malignancy cannot be detected in this study. Further study with larger sample size is required. Secondly, this study was conducted in retrospective aspect. Some data or information may not available. However, the important data such as pathologic data and genetics data were reviewed.

Conclusion

In conclusion, some aspects of characteristics of BRCA 1 and 2 mutation patients who were assigned to perform RRSO in this study is different from previous study but it may be an informative data of other newly opened genetic testing services. There was no occult fallopian tube cancer found in SEE-FIM protocol after RRSO. In premenopausal women, menopausal symptoms may develop after RRSO. Further study with larger sample size is required.

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ORIGINAL ARTICLE

Clinical Features and Histopathological Characteristics of Patients with Appendiceal Mucinous Neoplasms in Siriraj Hospital

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Abstract

Background: Mucinous neoplasm is the most common tumor of appendix. The current WHO classification provides criteria for histologic diagnosis, but correlation with clinical behavior and management is still controversial.

Objective: The purpose of this study is to determine the pathologic features that predict the clinical outcome of patients with mucinous appendiceal neoplasms.

Materials and methods: We retrospectively reviewed clinical data and surgical pathology of the appendiceal mucinous neoplasm from January 2009 to April 2018 in Siriraj hospital.

Results: There was a female preponderance (F/M: 2.7:1). Most patients presented with increased abdominal size. Two most common histologic diagnoses were low-grade appendiceal mucinous neoplasm (LAMN) (76.4%) and mucinous adenocarcinoma (ADC) (21.2%). Most common gross surgical finding was ruptured appendix with intraabdominal metastasis (52 cases, 61.2 %). Omentum is the most common metastatic site. Significant recurrence-free survival difference was observed between M0 and M1 diseases, but not between histologic diagnosis. A case with TisM0 status with late metastasis was observed.

Conclusion: The recurrence-free survival is correlated with the M stage of the disease, not the histologic diagnosis. Early stage LAMN may have metastatic potential.

Keywords: Appendiceal tumor, LAMN, Mucinous neoplasm, Adenocarcinoma, Pseudomyxoma peritonei

Introduction

Appendiceal tumors are rare neoplasms, comprising approximately 1% of appendectomy specimens. The major categories of primary appendiceal neoplasms include epithelial tumors (subclassified as mucinous tumors, neuroendocrine tumors, and mixed glandular and endocrine tumors), mesenchymal tumors, and lymphomas [(1)]. The most common type of non-carcinoid tumors of the appendix is mucinous appendiceal neoplasm [(2,3)].

The pathologic classifications of appendiceal mucinous neoplasms (AMN) are controversial due to the discrepancy between the histopathological findings and clinical behaviors. Previously, appendiceal mucinous neoplasms were classified as either adenomas or adenocarcinomas based on histologic evidence of invasive growth [(1)]. Nowadays, appendiceal mucinous neoplasms and mucinous adenocarcinomas were diagnosed base on cytoarchitectural classification [(4)], which was adopted by the World Health Organization classification in 2019[(5)].

The most significant complication of appendiceal mucinous neoplasm is the development of pseudomyxoma peritonei. Pseudomyxoma peritonei is the detection of mucinous neoplastic cells and extracellular mucin in the visceral and parietal peritoneum. Even the appendiceal mucinous neoplasm without malignant features, mucin and mucinous neoplastic cells can spill into the peritoneal cavity. These mucinous neoplastic cells can continue to proliferate, developing pseudomyxoma peritonei [(6)]. This peritoneal disease is an important factor affecting treatment and survival [(7)]. Treatment of pseudomyxoma peritonei of appendiceal origin includes repeated drainage of the mucinous ascites, and serially debulking surgeries. The cytoreductive surgery (CRS) combined with heated intraperitoneal chemotherapy (HIPEC) has been advocated by many authors [(6-10)].

Most published surgical literature suggests that simple appendectomy is sufficient for appendiceal tumors with local disease [(11)]. Right hemicolectomy is considered in selective cases of tumors involving the peri-appendiceal area, tumor size larger than 2 cm, high-grade histology, tumor invading through the muscularis propria and margin involvement after appendectomy [(12)].

In this work, we aimed to describe and evaluate the clinical features, histopathologic characteristics, tumor staging, and clinical outcomes of patients diagnosed with appendiceal mucinous neoplasms in Siriraj Hospital.

Materials and Methods

This retrospective study was approved by an Institutional Review Board. A list of patients older than 18-year-old diagnosed with appendiceal mucinous neoplasm (including

mucinous adenocarcinoma) from January 2009 to April 2018 in Siriraj Hospital were retrieved from the computerized pathology database. Recorded variables including age, gender, date of diagnosis, surgical finding, date and type of surgical procedure (surgery alone vs. CSR with HIPEC), lymph node dissection, chemotherapy, date of last follow-up, and date of recurrence (if occurred) were obtained from patients' medical records. Recurrence was defined by the detection of tumor implants on computed tomography (CT) scan during follow-up or identification of such implants at the time of subsequent surgery. Histopathologic findings were reviewed by a pathology resident (PA) and a gastrointestinal pathologist (AP), using diagnostic criteria from the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual and WHO classification 2019.[5, 13] The histopathologic diagnosis was recorded as; low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasm (HAMN), moderately differentiated mucinous adenocarcinoma (MD-ADC) and poorly differentiated mucinous adenocarcinoma (PD-ADC). Grade of tumor, tumor extension, nodal metastasis, intraperitoneal and organ metastasis were also recorded.

Histopathological evaluation

The histopathologic characteristics of LAMN (Fig 1) are filiform or villous mucinous epithelium with tall cytoplasmic mucin vacuoles and bland nuclei. The tumor generally shows non-infiltrative pushing border with extracellular mucin. The appendiceal wall is fibrotic, hyalinized, and calcified[5]. The features of the HAMN (Fig 2) are similar to those of LAMN, with added piling up of epithelial cells in micropapillary or cribriform pattern. The high-grade cytologic features are enlarged, hyperchromatic, pleomorphic nuclei, and numerous atypical mitotic figures[5].

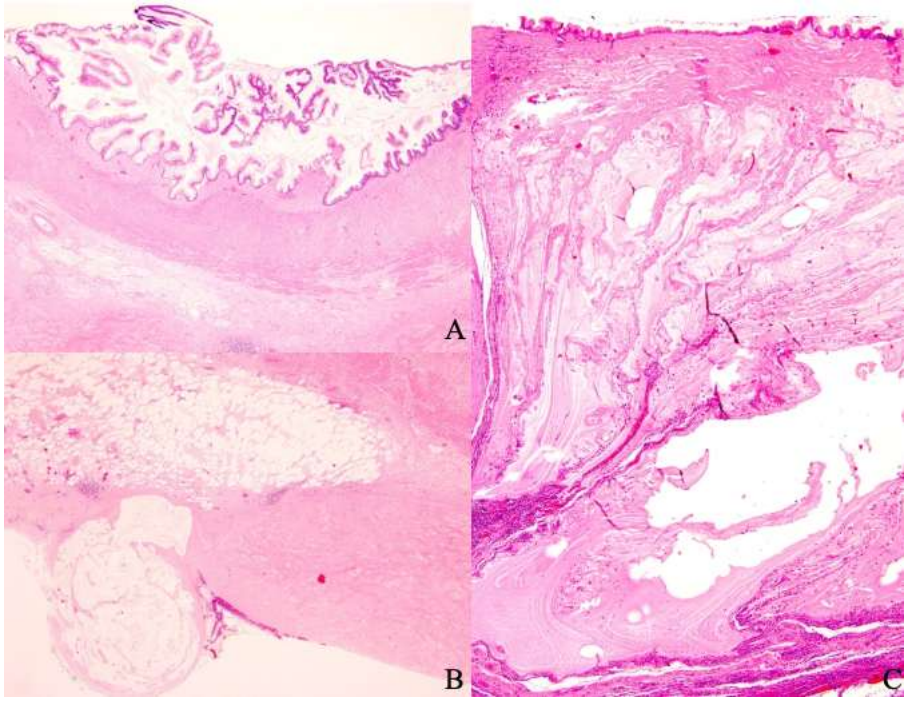

Figure 1: A) LAMN (Tis) demonstrates pushing growth pattern into the wall of appendix. (H&E x40 magnification) B) LAMN (T4a) shows mucin invade through serosal surface. (H&E x40 magnification) C) LAMN (T3) shows mucinous material extending into the subserosa, but does not perforate through the serosal surface. (H&E x40 magnification)

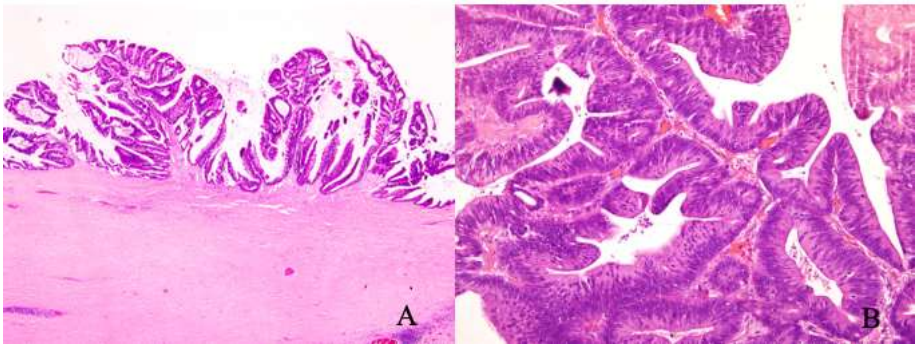

Figure 2: A) HAMN shows papillary structure without infiltrative invasion. (H&E, x40) B) Tumor cells demonstrate enlarged, hyperchromatic, and pleomorphic nuclei. Mitotic figures are frequent. (H&E, x400)

A staging system for LAMN is based on AJCC 2017[13]. LAMNs that invade just mucosa but not through the muscularis propria are assigned to Tis LAMN category. The categories T1 and T2 are not used for LAMN classification. The tumors that involve the subserosa are assigned to the T3 category. Tumors (including acellular mucin) that penetrate the serosal surface are assigned to the T4a category. Tumors directly invade other organs are assigned to the T4b category. The presence of intraperitoneal acellular mucin without identifiable tumor cells is staged as M1a, while the intraperitoneal metastasis with mucinous tumor cells is staged as M1b. The extraperitoneal metastasis is staged as M1c. The staging of the HAMN is similar to LAMN

The histopathologic characteristics of mucinous adenocarcinoma (Fig 3) are tumor cells infiltrating the wall of appendix with desmoplastic stromal reaction along with extracellular mucin. The carcinoma cells are columnar cells with hyperchromatic nuclei and mucinous cytoplasm. The extracellular mucin can be extensive, resulting in mucin pools with floating strips or clusters of mucinous epithelial cells [5].

The mucinous adenocarcinoma staging is similar to the traditional colorectal adenocarcinoma.

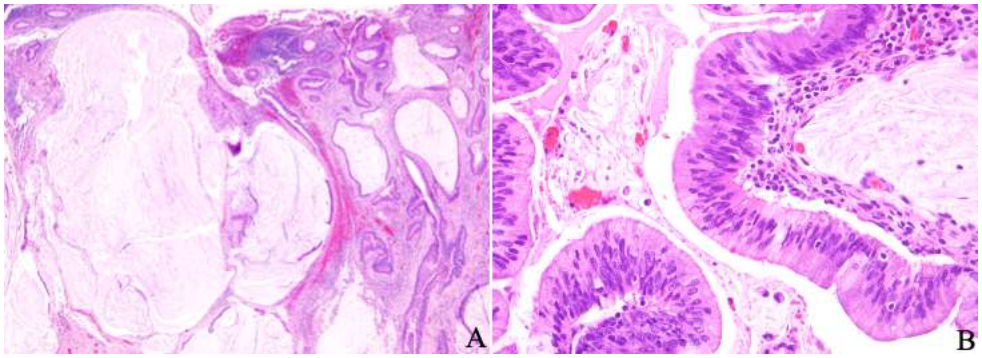

Figure 3: A) MD-ADC shows gland-forming tumor with abundant mucin and infiltrative invasion. Desmoplastic stroma is identified (H&E, x40) B) Neoplastic columnar epithelial cells containing hyperchromatic nuclei (H&E, x400)

Statistical analysis

Continuous variables were presented as the median value or average value and standard deviations. Nominal variables were presented as the frequency of events (%). The categorical variables were compared and the differences were determined by either chi-square or Fisher's exact test, depends on the data distribution. Disease-free survival (DFS) was defined as the number of weeks between the date of diagnosis and the date of last follow-up (right-censored) or the date of disease recurrence, whichever occurred first. The Kaplan-Meier method was used to construct disease-free survival curves, and significance among groups was determined using log-rank tests (univariate). All statistical hypothesis tests were performed using IBM SPSS Statistics version 22.0 for Windows and R Studio version 1.2.5033. A p-value < 0.05 was considered statistically significant.

Results

Eighty-five patients from January 2009 to April 2018 had confirmed appendiceal mucinous neoplasms during the review. Clinical and histopathological characteristics of these patients were listed in Table 1. The median age of patients at the time of diagnosis was 61 years (range 31–86 years). The female to male ratio in this cohort was 2.7:1. The most common clinical presentation was increased abdominal size (33 patients, 38.8 %), followed by pelvic mass (16 patients, 18.9%), and abdominal pain (13 patients 15.3%). Twelve patients (14.1%) were asymptomatic and were discovered incidentally during other surgical procedures.

Low-grade appendiceal mucinous neoplasm (LAMN) was the most common mucinous neoplasms diagnosed in 65 patients (76.5 %), followed by moderately differentiated mucinous adenocarcinoma (MD-ADC) diagnosed in 17 patients (20%). At the time of surgery, the majority of patients (58 patients, 68.2%) showed tumor ruptured through the appendix. Twenty-seven patients (31.8%) had tumor confined in the appendix. Once the tumor ruptures through appendiceal wall, almost all cases (53, 62.3%) showed synchronous peritoneal metastasis. The most common metastasis site (40, 47.1%) was omentum followed by ovary and peritoneum.

Twenty-eight patients (32.9%) in this study were treated with CSR plus HIPEC either at the first operation or at the time of recurrence.

Table1: Clinical and histopathological characteristics of 85 patients with appendiceal mucinous neoplasms

Characteristics	N (%)
Age Median, years (range)	61 (31-86)
Sex Female: Male	62:23
Clinical Presentation	
Increased abdominal size	33 (38.8)
Pelvic mass	16 (18.9)
Abdominal pain	13 (15.3)
Incidental finding	12 (14.1)
Presented as appendicitis	11 (12.9)
Diagnosis	
Low-grade appendiceal mucinous neoplasm	65 (76.5)
Moderately differentiated mucinous carcinoma	17 (20)
High-grade appendiceal mucinous neoplasm	2 (2.4)
Poorly differentiated mucinous carcinoma	1 (1.2)
Pathologic tumor extension	
Tumor confined in appendix	27 (31.8)
Tumor ruptured through appendix without metastasis	5 (5.9)
Tumor ruptured through appendix with metastasis (1^{st} presentation or recurrence)	53 (62.3)
Organ metastasis	
Omentum	40 (47.1)
Ovary	33 (38.8)
Peritoneal	16 (18.8)
Uterus	1 (1.2)
Spleen	9 (10.6)
Colon	2 (2.4)
Gallbladder	2 (2.4)
Received HIPEC (at 1^{st} operation or when recurrence)	28 (32.9)
Received chemotherapy	16 (18.8)

TNM staging of 65 patients with LAMN was listed in Table 2. More than half of LAMN (58.9%) showed metastasis (M1) at presentation. None of them showed nodal metastasis. Around forty-six (46.2) percent of patients were documented as T4a. Eleven patients (16.9%) had disseminated peritoneal disease (M1b) with unrecognizable appendiceal structure. These cases were assumed to be pT4a in the subsequent analysis as the tumor cells must penetrate the serosal surface in order to obliterate its structure. All 24 patients with LAMN confined in the appendix, either Tis or T3, showed no metastasis at diagnosis (M0).

Table 2: TMN staging of 65 patients with low-grade appendiceal mucinous neoplasm

T stage N (%)		N stage		M stage		
		N0	N1	M0	M1a	M1b
Tis	19 (29.2)	19 (100)	0	19 (100)	0	0
T2	0 (0.0)	0	0	0	0	0
T3	5 (7.7)	5 (100)	0	5 (100)	0	0
T4a	30 (46.2)	30 (100)	0	6 (20)	2 (6.7)	22 (73.3)
NA (presumed T4a)	11 (16.9)	NA	NA	0	0	11 (100)
Total	65 (100)	54 (83)	0	30 (46.1)	2 (3.1)	33 (50.8)

TNM staging of 17 patients with MD-ADC was listed in Table 3. Majority of MD-ADC (88.2%) showed metastasis (M1) at presentation. A large majority of these patients (76.4%) were documented as T4a. Two patients (11.8%) were in M1b status with obliterated appendiceal structure similar to LAMNs. These cases were also assumed to be pT4a.

Table 3: TMN staging of 17 patients with moderately differentiated mucinous adenocarcinoma

T stage N (%)		N stage		M stage		
		N0	N1	M0	M1a	M1b
Tis	0 (0.0)	0	0	0	0	0
pT2	1 (5.9)	1 (100)	0	1 (100)	0	0
pT3	1 (5.9)	1 (100)	0	1 (100)	0	0
pT4a	13 (76.4)	12 (92.3)	1 (7.7)	0	1 (7.7)	12 (92.3)
NA (presumed T4a)	2 (11.8)	NA	NA	0	0	2
Total	17 (100)	14	1	2 (11.8)	1 (5.9)	14 (82.3)

There were 2 HAMNs and 1 PD-ADC; all of them were treated with surgery without additional adjuvant therapy. The treatments given to patients with LAMNs and MD-ADCs were summarized in figure 4. Patients diagnosed with MD-ADC in our cohort were more likely to receive adjuvant treatment than LAMN (X^2= 8.0267, degree-of-freedom = 3, p-value = 0.045). However, there were more patients with M1 status in MD-ADC group compared to the LAMN group (88.2% vs. 53.9%, respectively). The significance difference was observed only in the M0 group (Fisher's exact test, p-value = 0.0121) but not in the M1 group (p = 0.88).

Comparing disease-free survival by the Kaplan-Meier method, there was a significant difference in disease-free survival between the M0 and M1 diseases, regardless of the histologic diagnosis (p = 0.006) (Figure 5A). However, no significant difference in disease-free survival among M1 diseases between AMN and ADC (p = 0.2) was observed (Figure 5B).

There was a patient presented with abdominal pain which underwent right hemicolectomy and was diagnosed with LAMN (TisM0). Interestingly, at day 938 after initial treatment, the patient came back with abdominal distension and pseudomyxoma peritonei

was documented. However, the patient refused further treatment. This result demonstrated that aggressive behavior is possible even in LAMN (TisM0).

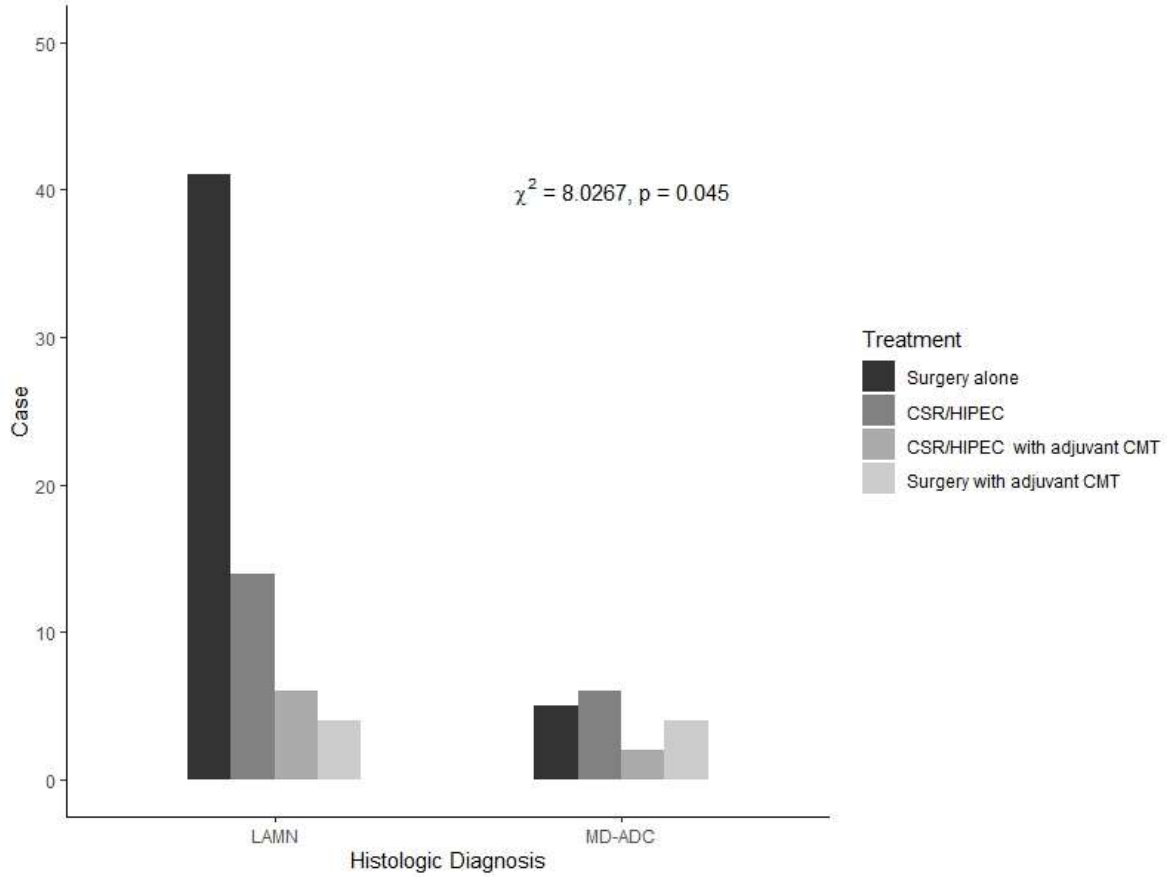

Figure 4: Adjuvant treatment based on histopathologic diagnosis

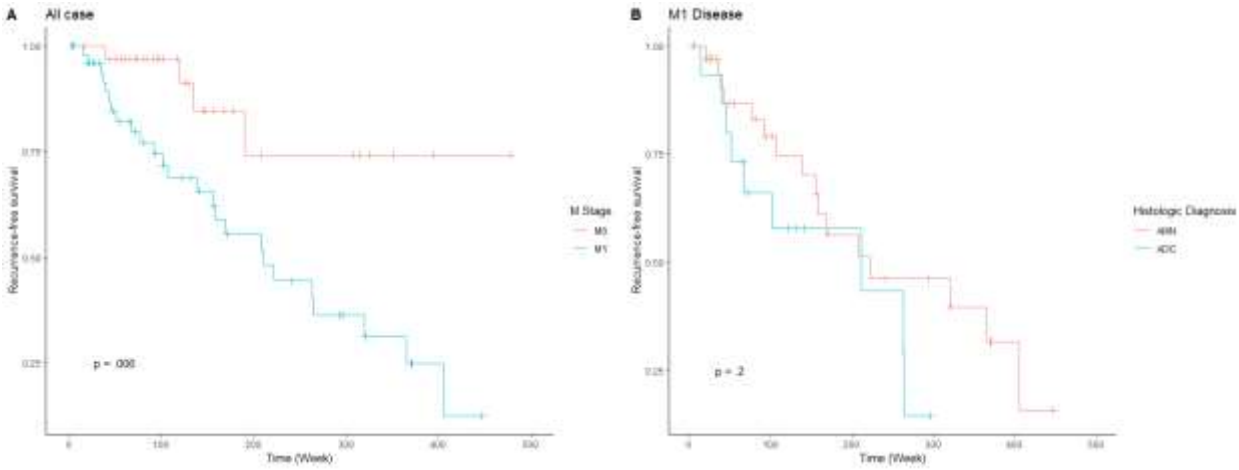

Figure 5: Recurrence- free survival of M stage and recurrence- free survival of M1 stage between AMN and ADC

Discussion

Appendiceal mucinous neoplasms are rare. The findings in this study correspond with those published in the literature. Appendiceal mucinous neoplasms occur in 5th to 6th

decades of life [10, 14] with female preponderance [13, 15]. The clinical presentation varies from early-stage presented with acute-appendicitis like symptoms [16] to advanced-stage presented with increasing abdominal girth due to the accumulation of mucinous ascites in the peritoneum [17]. Majority of patients in this study presented with advanced stage, suggesting that clinically silence early primary tumor is common.

The most common appendiceal mucinous neoplasm in this study was LAMN, followed by MD-ADC. Metastatic disease (M1) at presentation was very common in MD-ADC and common in LAMN. Our result suggested that the disease (recurrence)-free survival depends on M staging rather than the histologic diagnosis. During gross examination, entire submission of appendix and extensive sampling of all visible intraperitoneal lesion are highly recommended, since identification of mucinous neoplastic cells in both primary tumor and metastatic lesion affects the patients' staging and prognosis. Importantly, as the presence of pocket of mucin without neoplastic cell along the peritoneal surface is considered a pT4a lesion, careful specimen handling during section through the appendix must be performed to prevent carry-over of mucin to the serosa which may lead to over-staging for T4a.

CSR/HIPEC without pre-operative systemic chemotherapy is recommended for LAMN with intraperitoneal metastasis. The systemic pre-operative chemotherapy followed by CSR/HIPEC is recommended in ADC [16]. However, in practice, the pathological examination from surgical specimen of appendix is necessary in order to confirm the diagnosis. The consideration of chemotherapy preoperatively would not be practical. In this study, the patient diagnosed with ADC were more likely to receive adjuvant chemotherapy comparing to those diagnosed with AMN. However, this result may be contributed by the fact that there were more ADC patients with M1 disease than AMN patients. When the M0 and M1 patients were analyzed separately, there was no significant difference in the M1 group. The significant difference was observed only in the M0 group, in which both MD-ADC (one pT2 and one pT3) patients received adjuvant therapy. However, the number of MD-ADC in M0 category is low and the result should be used with caution.

Intraperitoneal recurrence is common in appendiceal mucinous neoplasms, even with adjuvant treatments. Our study demonstrated that disease-free survival is determined by M status rather than histologic diagnosis. This is due to an artificial nature of the histologic classification which can be influenced by other factors such as sampling error and subjectivity of morphologic evaluation. As the result showed similar disease-free survival between AMN and ADC diagnosis in patients with M1 status.

In this study, there was a single patient presented with localized low-grade disease LAMN (TisM0) but subsequently recurred as pseudomyxoma peritonei after two years. This suggests that even localized AMN may have recurrence/metastatic potential. Patients diagnosed with early-stage AMN may need long-term monitoring. The benefit of initial adjuvant chemotherapy in this group of patient remains to be proven [16].

This study is with limitations. All the cases in our study were reviewed and analyzed retrospectively. Many of the early cases (2009-2013) were from the period in which CSR/HIPEC was not yet available. The majority of the treatment decision was done using the pre-operative clinical and radiological data, which may not be influenced by the histologic classification performed by pathologists. Several clinical parameters may influence the treatment decision and outcome that were not included in the analysis such as, patient's co-morbidity, functional status, desire for adjuvant treatment, etc. The distribution in T-staging was also skewed toward higher stage due to the nature of disease and clinical presentation. The artificial nature of the histologic diagnosis also plays a role as Tis can only be assigned to L/HAMN, not ADC. Biological classification, possibly with mutation or expression profile, may be able to clarify this issue further.

Another limitation is the nature of the primary tumor in cases with a disseminated intraperitoneal disease without an identifiable primary structure. In females, ovarian primary is a possibility, 16.6 % in pseudomyxoma peritonei case [(18)]. The study relied on pre-operative diagnosis and intra-operative examination by the surgeons to exclude the ovarian primary without definite histologic examination. The study also assumed pT4aM1 status in patients without an identifiable appendix. This relied heavily on the thoroughness of the gross examiner and histopathologist which can vary significantly between institute.

Conclusion

In conclusion, appendiceal mucinous neoplasms are uncommon. Majority of patients present in advanced stage with intraperitoneal metastasis. Most common histologic diagnoses are low-grade appendiceal mucinous neoplasm (LAMN) and Moderately Differentiated Adenocarcinoma (MD-ADC). Patients with adenocarcinoma diagnosis are more likely to receive adjuvant treatment, either CSR/HIPEC or chemotherapy, or both. Our study shows that the disease-free survival of the patient is influenced by M staging rather than histologic diagnosis. We also demonstrate that the localized LAMN may have late recurrence/metastasis even without any evidence of spreading at the time of initial surgery/diagnosis, and long term follow up is warranted in all AMN cases.

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ORIGINAL ARTICLE

Frequency of different tumor types diagnosed in Whipple specimen in a local population

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Abstract

Background: Whipple procedure is performed for the diagnosis and management of malignant and benign conditions involving the head of the pancreas and surrounding structures.

Objective: The purpose of this study is to determine the frequency of different tumor subtypes diagnosed in Whipple specimen in a local population.

Materials and Methods: 156 cases were selected. Both male and female patients with age between 16-75 years were selected. All autolyzed/unfixed samples (samples in weak formalin) were excluded. The histological preparation was performed by classical method for inclusion in paraffin followed by hematoxylin eosin staining. Then subtype of tumor was also recorded.

Results: In this study 40(25.6%) patients showed pancreatic adenocarcinoma, 27(17.3%) duodenal adenocarcinoma, 20(12.8%) ampullary carcinoma, 35(22.4%) CBD cholangiocarcinoma, 5(3.2%) other type of lesion and neuroendocrine tumor was found in 29(18.59%) patients.

Conclusion: The most common diagnosis in Whipple specimen was pancreatic adenocarcinoma followed by CBD cholangiocarcinoma, neuroendocrine tumor, duodenal carcinoma and ampullary carcinoma

Keywords: Whipple procedure, pancreatic adenocarcinoma, cholangiocarcinoma, ampullary carcinoma, neuroendocrine tumor.

Introduction

Pancreaticoduodenectomy or Whipple procedure is performed for the diagnosis and management of malignant and benign conditions involving the head of the pancreas and surrounding structures. It is the most common surgery to remove tumors of the head of the pancreas, ampulla, distal common bile duct, or periampullary duodenum. For accurate diagnosis, evaluation of tumor origin, margin status, determining staging, and other important Prognostic factors such as perineural invasion and lymphovascular invasion the most critical first step in pathological evaluation is to correctly gross the surgical specimen and submit appropriate tissue sections for histologic assessment.

About 5% of the gastrointestinal malignancy is constituted by the ampullary and periampullary carcinoma [(1)]. There are several principles for creating a particular cancer staging system that are critical for the system to be clinically applicable. Special attention is required with regard to margins and lymph node status while dealing with a Whipple specimen, as these are two of the most important prognostic factors in pancreatic, ampullary, and periampullary adenocarcinoma. The American Joint Committee on Cancer Staging Manual represents the standard for classifying patients with pancreas and hepatobiliary cancers, predicting prognosis, and guiding treatment decisions.

Pathologic examination of resected pancreaticoduodenectomy specimens reveal that 40-60% of malignant tumors are adenocarcinomas of the head of the pancreas, 10-20% are adenocarcinomas of the ampulla of Vater, 10 % are distal bile duct adenocarcinomas, and 5-10 % are duodenal adenocarcinomas [(2)].

It has been reported that 86.3% patients had malignant and 13.7% patients had benign lesions. Among malignant lesions 61.4% were ampullary carcinomas, 27.3% were pancreatic carcinomas and 11.4% were cholangiocarcinomas.

Another study found that malignant tumor was present in 88.57% cases whereas 11.43% cases harbored benign lesions. Periampullary mixed carcinoma was the predominant tumor (34.28%) followed by periampullary duodenal (20%), ampullary (14.28%), pancreatic adenocarcinoma (11.42%) and distal cholangiocarcinoma (5.71%) [(3)].

Rationale of this study is to determine the frequency of different malignant tumor types diagnosed in Whipple specimen. Through literature, it has been noticed that there is variability in the frequency of different malignant tumors diagnosed in Whipple specimens. But there is no local evidence found in literature that can help us to determine the extent of problem in local population. So, we want to study the prevalence of different malignant tumor types in the local setting. This will help us to obtain local evidence and with the help of results obtained through this study, we will recommend the surgeons to plan the treatment protocols according to the commonness of the type of tumor.

The pancreas is a retroperitoneal organ and located within the C-loop of the duodenum. It is divided into the head, uncinate process, neck, body, and tail. The head and the uncinate process are supplied by superior and inferior pancreaticoduodenal arteries, which

are branches from the gastroduodenal artery and middle colic artery. The neck, body, and tail of the pancreas receive blood supply from the splenic artery through the dorsal pancreatic artery, greater pancreatic artery, and transverse pancreatic artery. The head of the pancreas is primarily drained by the four pancreaticoduodenal veins, whereas they drain into the superior mesenteric vein or portal vein. The neck, body, and tail of the pancreas have venous drainage into the splenic vein. The main duct of the pancreas (Wirsung) begins in the tail, runs the entire length of the pancreas, and opens into the second part of the duodenum together with the bile duct on the major duodenal papilla.

There are several critical anatomical considerations in pancreatic surgery. The pancreas shares the same blood supply with the C-loop of the duodenum, necessitating the removal of the C-loop of the duodenum together with the pancreas. The uncinate process which arises from the lower part of the head of the pancreas extends superiorly and posteriorly behind the superior mesenteric vein is recognized as essential surgical anatomy. Tumor involving the uncinate process is associated with vascular invasion and poor prognosis compared with non-uncinate process pancreas cancer [(4)].

Variation in vascular anatomy in this region is uncommon compared to biliary variation; however, there is some relevant variation that needs to be borne in mind. Replaced right hepatic artery arising from the superior mesenteric artery occurs around 12% of the population. In this case, the native hepatic artery is absent. The patient can also have an accessory right hepatic artery, which indicates the presence of the extra right hepatic artery together with the native right hepatic artery. The neck of the pancreas lies behind the portal vein confluence and is also the origin of the superior mesenteric artery. Superior mesenteric vein located to the right of superior mesenteric artery; thus, superior mesenteric vein is the first vascular structure that one will encounter in the duodenal curvature. In the Cattell-Braasch maneuver, where the right-sided viscera is rotated to the left, the critical structure is inferior vena cava and abdominal aorta. The left renal vein crossing across the aorta to drain into inferior vena cava is a crucial anatomical observation. The tortuous splenic artery runs along the superior border of the pancreas. The splenic vein runs posteriorly to the body of the pancreas.

Pancreatic cancer is the tenth most common cancer in men and the ninth most common in women, but it is the fourth leading cause of cancer deaths, being responsible for 8% of all cancer-related deaths. Approximately 75% of all pancreatic carcinomas occur within the head or neck of the pancreas, 15-20% occur in the body of the pancreas, and 5-10% occur in the tail.

Although pancreatic cancer accounts for only about 3% of all cancers in the United States, it is the fourth leading cause of cancer deaths in both men and women, being responsible for 7% of all cancer-related deaths. The average lifetime risk of developing pancreatic cancer is about 1 in 67.5

Of all pancreatic cancers, 80% are adenocarcinomas of the ductal epithelium. Only 2% of tumors of the exocrine pancreas are benign. Five Less common histologic appearances of exocrine pancreatic cancers include giant cell carcinoma, adenosquamous carcinoma, microglandular adenocarcinoma, mucinous carcinoma, cystadenocarcinoma, papillary cystic carcinoma, acinar cystadenocarcinoma, and acinar cell cystadenocarcinoma. Very rarely, primary connective tissue cancers of the pancreas can occur. The most common of these is primary pancreatic lymphoma [(5)].

Worldwide, pancreatic cancer ranks 11th in incidence but 7th as a cause of cancer death. The age-standardized rate (ASR) incidence ranges widely, from 7.7 per 100,000 population in Europe to 2.2 per 100,000 population in Africa. Among individual countries, ASRs range from 0.81 per 100,000 in males in India to 15.3 per 100,000 in males in Latvia and the Republic of Moldova [(6)].

Although pancreatic cancer constitutes only about 3% of all cancers in the United States, it is the fourth leading cause of cancer deaths in both men and women, being responsible for 8% of all cancer-related deaths. The American Cancer Society estimates that in the United States in 2020, about 47,050 people (24,640 men and 22,410 women) will die of pancreatic cancer. During 2008 to 2017, the death rate for pancreatic cancer increased slightly (by 0.4% per year) in whites and decreased slightly (by 0.5% per year) in blacks.

Surgical resection is the only treatment that offers a potential cure of pancreatic cancer and the addition of chemotherapy in the adjuvant setting has been shown to improve survival rates. There have been some optimistic results showing a further improvement in survival with the administration of chemo-radiotherapy in the neo-adjuvant setting but further work is needed to identify which group of patients will benefit the most.

Pancreatico-duodenectomy (Whipple procedure), distal or total pancreatectomy are the surgical options for the resection of pancreatic cancer depending on the anatomical location of the tumor or tumors. Reorganization of healthcare services and restriction of these procedures to high volume centers has improved outcomes as surgeon's expertise increases. Innovations in technology and operative technique have sought to further reduce adverse outcomes and improve survival. The aim of surgical resection is to achieve an R0 resection as this is associated with a significantly improved survival compared to R1 resections. Neo-adjuvant treatment and vascular resections have been employed in an attempt to increase the rate of microscopic clearance.

Pancreatic adenocarcinoma is a lethal condition with poor outcomes and an increasing incidence. Pancreatic cancer is ranked as the 14th most common cancer and the 7th highest cause of cancer mortality in the world. The highest age-standardised incidence is seen in Europe and North America, and the lowest in Africa and South Central Asia.

Although the majority of small bowel adenocarcinomas arise in the duodenum, duodenal adenocarcinoma (DA) still represents less than 1% of all gastrointestinal cancers.

Not surprisingly, given the rarity of the disease, there is limited data to guide treatment decisions. Early studies grouped DA with other periampullary tumors (pancreatic, ampullary, distal bile duct) when discussing their management options. However, in general, DA has a more favorable outcome. For example, compared to some other periampullary malignancies, DA is more likely to be amenable to curative resection and has more favorable long-term outcomes.

Small bowel malignancies are relatively rare, accounting for only 2% of all gastrointestinal cancers in the United States. Among small bowel tumors, most malignancies arise from the ileum, followed by the duodenum and lastly the jejunum. While most tumors of the ileum are neuroendocrine in origin, adenocarcinoma is the most common duodenal cancer. One large population-based analysis found the duodenum to be the location of 55.7% of adenocarcinomas of the small bowel. The majority of DA arise in the second portion of the duodenum, followed by D3/D4, with cancers of the first portion of the duodenum, especially the duodenal bulb, extremely rare.

Ampullary cancer is a rare malignant disease, occurring in approximately 0.2% of all gastrointestinal tumors. Its localization characteristic symptoms like jaundice and pain usually occur earlier compared with other malignant pancreatobiliary tumors like pancreatic cancer. This is possibly the reason for the better prognosis of ampullary carcinomas with a reported 5-year survival rate of 45% in resected patients. For diagnosis, computed tomography, esophagogastroduonoscopy, endoscopic guided biopsy, endosonography, endosonography-guided biopsy, and ultrasound are useful. The current gold standard of treatment is the oncological resection of the tumor together with lymph node dissection. For this reason, in most cases a pancreatic head resection is necessary. Different studies have shown that the lymph node status in ampullary carcinoma is an important prognostic predictor. The use of adjuvant chemotherapy in patients with resected ampullary cancers has not been proven in prospective randomized clinical trials yet. Furthermore, multiple studies have shown no benefit in overall survival or disease-free survival for adjuvant treatment. According to the histopathologic characteristics, different subtypes of ampullary carcinomas are described. The pancreatobiliary subtype arises from simple mucinous epithelium of the distal common bile duct, the distal pancreatic duct, or common ampullary duct with simple or branching glands and small solid cell-nests enclosed by desmoplastic stroma. This epithelium builds the mucosal lining of the ampulla. One theory is that the degeneration of the epithelium could follow an analogous dysplasia-adenocarcinoma sequence akin to pancreatic intraepithelial neoplasia. From the intestinal mucosa, which covers the papilla, originates the intestinal type with well-formed tubular glands, complex cribriform areas, and solid nests. This epithelium might be arise through an adenoma-dysplasia-adenocarcinoma sequence related to colon cancer. The mixed subtype is described as a tumor consisting of more than 25% of each differentiation or as a tumor consisting of hybrid differentiation like intestinal architecture with

pancreatobiliary cytology. When comparing the subtypes, they differ in prognosis with 5-year survival rates ranging from 20% for the pancreatobiliary subtype to 88% for the intestinal subtype for resected patients [(4)]. Therefore, there is reason to believe that the prognosis of papillary carcinoma is related to the subtype.

Common bile duct cholangiocarcinoma is a rare disease in which malignant (cancer) cells form in the bile ducts. A network of tubes, called ducts, connects the liver, gallbladder, and small intestine. This network begins in the liver where many small ducts collect bile (a fluid made by the liver to break down fats during digestion). The small ducts come together to form the right and left hepatic ducts, which lead out of the liver. The two ducts join outside the liver and form the common hepatic duct. The cystic duct connects the gallbladder to the common hepatic duct. Bile from the liver passes through the hepatic ducts, common hepatic duct, and cystic duct and is stored in the gallbladder.

When food is being digested, bile stored in the gallbladder is released and passes through the cystic duct to the common bile duct and into the small intestine. Bile duct cancer is also called cholangiocarcinoma.

Neuroendocrine tumors (NETs) are neoplasms that arise from cells of the endocrine (hormonal) and nervous systems. They most commonly occur in the intestine, where they are often called carcinoid tumors, but they are also found in the pancreas, lung and the rest of the body.

Although there are many kinds of NETs, they are treated as a group of tissue because the cells of these neoplasms share common features, such as looking similar, having special secretory granules, and often producing biogenic amines and polypeptide hormones.

Whipple procedure is done for tumors of the periampullary region which include periampullary carcinoma, ampullary carcinoma, pancreatic tumors, tumors of the pancreatic duct, tumors of the common bile duct, duodenal carcinoma and sometimes for non-malignant conditions. This procedure involves removal of the head of the pancreas, part of the duodenum, part of the bile duct, the surrounding lymph nodes, the gallbladder and sometimes part of the stomach.

The main objective of this study is to determine the frequency of different tumor subtypes diagnosed in Whipple specimen in a local population. The outcome of this study will help to identify the commonest tumors.

Materials and Methods

This is a descriptive, cross-sectional study held in Sheikh Zayed Hospital Lahore over a duration of six months. The calculated sample size (collected by non-probability consecutive sampling) taking confidence level of 95% and margin of error of 5% and average prevalence of 9.25% is 156 and population proportion of pancreatic adenocarcinomas was 11.42%.

The biopsy specimens sent to histopathology department after whipple procedure were chosen for this study. Both males and females with age between 16-75 years were chosen. All poorly fixed specimens sent in weak formalin were excluded from this study.

After approval from institutional ethical committee, the 156 biopsy specimens fulfilling the inclusion criteria were enrolled in the study. All data was collected by using a proforma. The requisition forms sent from surgery department were retrieved along with other relevant investigations. The clinical parameters like age were recorded. The histological preparation was performed by classical method for inclusion in paraffin followed by hematoxylin-eosin staining. Then subtype of tumor was also recorded. All the data was recorded on the proforma.

Statistics for collected data was done by using IBM SPSS v. 21. Quantitative data like age & duration of symptoms was computed as mean + standard deviation. Frequency and percentage was computed for qualitative data like gender and subtype of tumor. Effect modifiers like age, gender and duration of disease were controlled through stratification. Post-Stratification chi-square test was applied by taking P value < 0.05 as significant.

Results

In this study total 156 patients were enrolled. The mean age of the patients was 54.49±10.50 years with minimum and maximum ages of 20 & 73 years respectively. Table 1

Table 1: Summary statistics of age (years)

Age (Years)	
N	156
Mean	54.49
Std. Deviation	10.50
Minimum	20
Maximum	73

Of 156 patients, 79(50.64%) were male and 77(49.36%) patients were female. Male to female ratio of the patients was 1.02:1 Fig 1

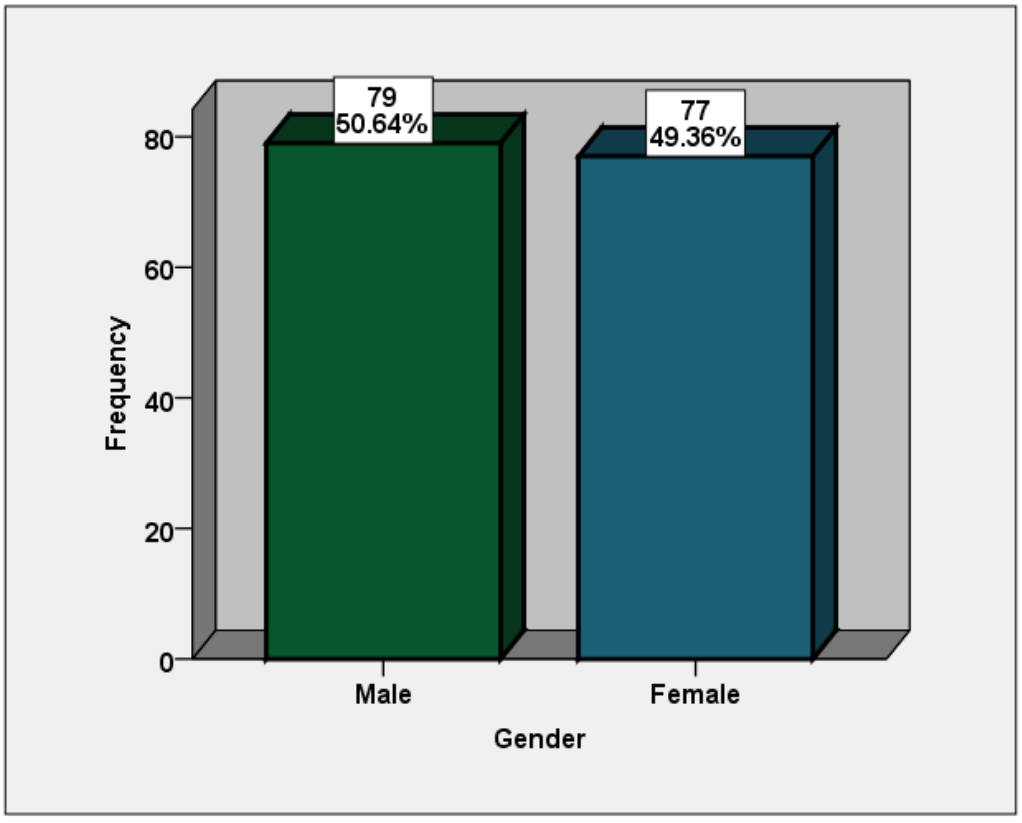

Fig 1: Frequency distribution of gender

In this study 40(25.6%) patients were diagnosed with pancreatic adenocarcinoma. Table 2, 4

In this study 27(17.3%) patients were diagnosed with duodenal adenocarcinoma. Table 2, 4

In this study 20(12.8%) patients were diagnosed with ampullary carcinoma. Table 2, 4

According to this study 35(22.4%) patients were diagnosed with CBD cholangiocarcinoma and 5(3.2%) patients were diagnosed with other type of lesion. Table 3, 5

Of 156 patients, neuroendocrine tumor was found in 29(18.59%) patients. Table 3, 5

In patients having age ≤ 50 years the pancreatic adenocarcinoma diagnosed in 9(14.8%) patients while in patients having age >50 years the pancreatic adenocarcinoma diagnosed in 31(32.6%) patients (p-value=0.013). In patients having age ≤ 50 years the duodenal adenocarcinoma diagnosed in 10(16.4%) patients while in patients having age >50 years the duodenal adenocarcinoma diagnosed in 17(17.9%) patients (p-value=0.809). Similarly In patients having age ≤ 50 years the ampullary carcinoma diagnosed in 11(18.0%) patients while in patients having age >50 years the ampullary carcinoma diagnosed in 09(9.5%) patients (p-value=0.119). Table 2

Table 2: Comparison of histopathological diagnosis between age groups

Histopathological Diagnosis		Age (Years)		Total	p-value
		≤ 50	>50		
Pancreatic Adenocarcinoma	Yes	9	31	40	0.013
		14.8%	32.6%	25.6%	
	No	52	64	116	
		85.2%	67.4%	74.4%	
Duodenal Adenocarcinoma	Yes	10	17	27	0.809
		16.4%	17.9%	17.3%	
	No	51	78	129	
		83.6%	82.1%	82.7%	
Ampullary Carcinoma	Yes	11	9	20	0.119
		18.0%	9.5%	12.8%	
	No	50	86	136	
		82.0%	90.5%	87.2%	

In patients having age ≤ 50 years the CBD cholangiocarcinoma was diagnosed in 09(14.8%) patients while in patients having age >50 years the CBD cholangiocarcinoma was diagnosed in 26(27.4%) patients (p-value=0.065). In patients having age ≤ 50 years the neuroendocrine tumors was diagnosed in 17(27.9%) patients while in patients having age >50 years the duodenal adenocarcinoma neuroendocrine tumors was diagnosed in 12(12.6%) patients (p-value=0.017). Table 3

Table 3: Comparison of histopathological diagnosis between age groups

Histopathological Diagnosis		Age (Years)		Total	p-value
		≤ 50	>50		
CBD cholangiocarcinoma	Yes	9	26	35	0.065
		14.8%	27.4%	22.4%	
	No	52	69	121	

		85.2%	72.6%	77.6%	
Neuroendocrine Tumors	Yes	17	12	29	0.017
		27.9%	12.6%	18.6%	
	No	44	83	127	
		72.1%	87.4%	81.4%	
Others	Yes	5	0	5	0.008
		8.2%	0.0%	3.2%	
	No	56	95	151	
		91.8%	100.0%	96.8%	

In male patients, the pancreatic adenocarcinoma diagnosed in 19(24.1%) patients. While in female patients the pancreatic adenocarcinoma diagnosed in 21(27.3%) patients (p-value=0.645). In male patients the duodenal adenocarcinoma diagnosed in 16(20.3%) patients. While in female patients the duodenal adenocarcinoma diagnosed in 11(14.3%) patients (p-value=0.325). Similarly In male patients the ampullary carcinoma diagnosed in 12(15.2%) patients. While in female patients the ampullary carcinoma diagnosed in 8(10.4%) patients (p-value=0.119). Table 4

Table 4: Comparison of histopathological diagnosis between genders

Histopathological Diagnosis		Gender		Total	p-value
		Male	Female		
Pancreatic Adenocarcinoma	Yes	19	21	40	0.645
		24.1%	27.3%	25.6%	
	No	60	56	116	
		75.9%	72.7%	74.4%	
Duodenal Adenocarcinoma	Yes	16	11	27	0.325
		20.3%	14.3%	17.3%	
	No	63	66	129	
		79.7%	85.7%	82.7%	
Ampullary Carcinoma	Yes	12	8	20	0.370
		15.2%	10.4%	12.8%	
	No	67	69	136	
		84.8%	89.6%	87.2%	

In male patients the CBD cholangiocarcinoma was diagnosed in 14(17.7%) patients. While in female patients the CBD cholangiocarcinoma was diagnosed in 21(27.3%) patients (p-value=0.153). In male patients the neuroendocrine tumors were diagnosed in 17(21.5%)

patients. While in female patients the duodenal adenocarcinoma neuroendocrine tumors were diagnosed in 12(15.6%) patients (p-value=0.341). Table 5

Table 5: Comparison of histopathological diagnosis between genders

Histopathological Diagnosis		Gender		Total	p-value
		Male	Female		
CBD cholangiocarcinoma	Yes	14	21	35	0.153
		17.7%	27.3%	22.4%	
	No	65	56	121	
		82.3%	72.7%	77.6%	
Neuroendocrine Tumors	Yes	17	12	29	0.341
		21.5%	15.6%	18.6%	
	No	62	65	127	
		78.5%	84.4%	81.4%	
Others	Yes	1	4	5	0.207
		1.3%	5.2%	3.2%	
	No	78	73	151	
		98.7%	94.8%	96.8%	

Discussion

Whipple pancreaticoduodenectomy is one of the most complex surgeries performed for the management of a variety of tumors involving the head of pancreas, ampulla of Vater, distal common bile duct or duodenum. Pathologic assessment of surgical specimens from pancreaticoduodenectomy (Whipple operation) needs special attention in order to accurately evaluate many factors that are prognostically important.

Tumors in the periampullary region arise in the papilla of Vater and the two centimeters surrounding it. Histologically, they could originate in the duodenal wall, pancreatic tissue, the wall of the distal bile duct or the structures of the ampullary complex. The papilla of Vater is formed by the confluence of the pancreatic duct and the bile duct and by the sphincter of Oddi that surrounds it.

In this study the most common diagnosis was pancreatic adenocarcinoma noted in 40(25.6%) patients followed by CBD cholangiocarcinoma noted in 35(22.4%) patients, neuroendocrine tumor in 29(18.59%) patients, duodenal carcinoma in 27(17.3%) patients and ampullary carcinoma noted in 20(12.8%) patients. Some of the studies are discussed below showing their results as.

Western literature reveals pancreatic adenocarcinoma to be the commonest finding in PD specimens. In a review of 650 pancreaticoduodenectomies, Yeo et al found 43% cases to be pancreatic adenocarcinoma. Distal common bile duct, ampullary, and duodenal cancers are less common than pancreatic cancer.

Pathologic examination of resected pancreaticoduodenectomy specimens reveal that 40–60% are adenocarcinomas of the head of the pancreas, 10–20% are adenocarcinomas of the ampulla of Vater, 10% are distal bile duct adenocarcinomas, and 5–10% are duodenal adenocarcinomas.

Studies reported that the most common histopathology of tumors in the ampulla of Vater is adenocarcinomas followed by adenosquamous and squamous cell carcinomas.
Pathologic examination of resected pancreaticoduodenectomy specimens reveal that 40-60% of malignant tumors are adenocarcinomas of the head of the pancreas, 10-20% are adenocarcinomas of the ampulla of Vater, 10 % are distal bile duct adenocarcinomas, and 5 - 10 % are duodenal adenocarcinomas.

It has been reported that 86.3% patients had malignant and 13.7% patients had benign lesions. Among malignant lesions 61.4% were ampullary carcinomas, 27.3% were pancreatic carcinomas, and 11.4% were cholangiocarcinomas. Another study found that malignant tumors present in 88.57% cases whereas 11.43% cases harbored benign lesions. Periampullary mixed carcinoma was the predominant tumor (34.28%) followed by periampullary duodenal (20%), ampullary (14.28%), pancreatic adenocarcinoma (11.42%) and distal cholangiocarcinoma (5.71%). Ramesh Dhakwa, Neeta Kafle have done a descriptive study in 35 patients who underwent Whipple procedure in a period of 36 months. They found that malignant tumor

was present in 31 cases and 4 cases had benign lesions. Among the malignant tumors, periampullary mixed carcinoma was the predominant tumor. Lymphovascular and perineural invasion varied in different tumor types [(3)].

Shifa et al in their study have reviewed 30 resected specimens of Whipple pancreaticoduodenectomy, out of which twenty-one had ampullary and periampullary carcinoma, the mean age incidence of ampullary carcinoma was 44 years [(1)].

In a report from Mayo Clinic, Smith et al. reviewed 484 patients who underwent Whipple procedure for suspected periampullary malignancy and found chronic inflammatory disease on final pathologic assessment in 24 patients (5%). vanGulik et al. described 220 patients who underwent Whipple and reported 6% benign findings. They suggested that at least 5% of benign finding is expected when performing PD for a suspected malignant disease. Given the grim prognosis of the pancreatic cancer this should not stop surgeons from performing the procedure on patients with clinically suspected malignancy but with no other confirming data [(6)].

Conclusion

This study concluded that the most common diagnosis in Whipple specimen was pancreatic adenocarcinoma followed by CBD cholangiocarcinoma, neuroendocrine tumor, duodenal carcinoma and ampullary carcinoma.

Acknowledgements

Not applicable.

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APPENDIX 1
INFORMATION FOR AUTHORS

All authors listed in a paper submitted to Asian Archives of Pathology (AAP) must have contributed substantially to the work. It is the corresponding author who takes responsibility for obtaining permission from all co-authors for the submission. When submitting the paper, the corresponding author is encouraged to indicate the specific contributions of all authors (the author statement, with signatures from all authors and percentage of each contribution can be accepted). Examples of contributions include: designed research, performed research, contributed vital new reagents or analytical tools, analysed data, and wrote the paper. An author may list more than one type of contribution, and more than one author may have contributed to the same aspect of the work.

Authors should take care to exclude overlap and duplication in papers dealing with related materials. See also paragraph on Redundant or Duplicate Publication in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" at http://www.icmje.org/index.html.

The submitted manuscripts will be reviewed by the members of the Editorial Board or the expert reviewers. At the discretion of the Editorial Board, the manuscripts may be returned immediately without full review, if deemed not competitive or outside the realm of interests of the majority of the readership of the Journal. The decision (reject, invite revision, and accept) letter will be coming from the Editorial Board who has assumed responsibility for the manuscript's review. The editor's decision is based not just on technical merit of the work, but also on other factors such as the priority for publication and the relevance to the Journal's general readership. All papers are judged in relation to other submissions currently under consideration.

Categories of Manuscripts

1. Letters to the Editor

The letters to the editor are the reactions to any papers published in AAP. These letters will be reviewed by the Editorial Board and sent to the authors of the original paper with an invitation to respond. Letters and eventual responses will be published together, when appropriate.

- *Word Count: 300 – 500 words (excluding references and figure or table legends)*
- *Abstract: Not required*
- *References: Maximum of 10*
- *Figure or Table: Maximum of 1 (if needed)*

2. Original Articles

The original articles are the researches describing the novel understanding of anatomical pathology, clinical pathology (laboratory medicine), forensic medicine (legal medicine or medical jurisprudence), molecular medicine or pathobiology. Systematic reviews, meta-analyses and clinical trials are classified as articles. The articles should be clearly and concisely written in the well-organised form (see ***Organisation of Manuscripts***): abstract; introduction; materials and methods; results; discussion; and conclusions. The manuscripts that have passed an initial screening by the Editorial Board will be reviewed by two or more experts in the field.

- *Word Count: 3,000 – 5,000 words (excluding abstract, references, and figure or table legends)*
- *Structured Abstract (see **Organisation of Manuscripts**): 150 – 200 words*
- *References: Maximum of 150*
- *Figures or Tables: Maximum of 6*

3. Review Articles

The review articles are generally invited by the Editor-in-Chief. They should focus on a topic of broad scientific interest and on recent advances. These articles are peer-reviewed before the final decision to accept or reject the manuscript for publication. Therefore, revisions may be required.

- *Word Count: 3,000 – 5,000 words (excluding abstract, references, and figure or table legends)*
- *Unstructured Abstract: 150 – 200 words*
- *References: Maximum of 150*
- *Figures or Tables: Maximum of 4*

4. Case Reports

AAP limits publication of case reports to those that are truly novel, unexpected or unusual, provide new information about anatomical pathology, clinical pathology (laboratory medicine) or forensic medicine (legal medicine or medical jurisprudence). In addition, they must have educational value for the aforementioned fields. The journal will not consider case reports describing preventive or therapeutic interventions, as these generally require stronger evidence. Case reports that involve a substantial literature review should be submitted as a review article. The submitted case reports will undergo the usual peer-reviewed process.

- *Word Count: 1,200 – 2,000 words (excluding abstract, references, and figure or table legends)*
- *Unstructured Abstract: 150 – 200 words*
- *References: Maximum of 20*
- *Figures or Tables: Maximum of 4*

5. Case Illustrations

Case illustrations are aimed to provide education to readers through multidisciplinary clinicopathological discussions of interesting cases. The manuscript consists of a clinical presentation or description, laboratory investigations, discussion, final diagnosis, and up to 5 take-home messages (learning points). Regarding continuous learning through self-assessment, each of the case illustrations will contain 3 – 5 multiple choice questions (MCQs) with 4 – 5 suggested answers for each question. These MCQs are placed after the final diagnosis and the correct answers should be revealed after the references. The questions and take-home messages (learning points) are included in the total word count. The manuscripts that have passed an initial screening by the Editorial Board will be reviewed by two experts in the field.

- *Word Count: 1,000 – 2,000 words (excluding references and figure or table legends)*
- *Abstract: Not required*
- *References: Maximum of 10*
- *Figures: Maximum of 2*
- *Tables: Maximum of 5*

6. Technical Notes

The technical notes are brief descriptions of scientific techniques used in the anatomical pathology, clinical pathology (laboratory medicine), forensic medicine (legal medicine or medical jurisprudence), molecular medicine or pathobiology. The submitted manuscripts are usually peer-reviewed.

- *Word Count: Maximum of 1,000 words (excluding references and figure or table legends)*
- *Abstract: Not required*
- *References: Maximum of 5*
- *Figures or Tables: Maximum of 2*

Organisation of Manuscripts

1. General Format

The manuscripts written in English language are preferable. However, Thai papers are also acceptable, but their title pages, abstracts, and keywords must contain both Thai and English. These English and Thai manuscripts are prepared in A4-sized Microsoft Word documents with leaving 2.54-cm (1-inch) margins on all sides. All documents are required to be aligned left and double-spaced throughout the entire manuscript. The text should be typed in 12-point regular Times New Roman font for English manuscript and 16-point regular TH SarabunPSK font for Thai manuscript.

The running titles of English and Thai manuscripts are placed in the top left-hand corner of each page. They cannot exceed 50 characters, including spaces between words and punctuation. For the header of English paper, the running title will be typed in all capital letters. The page number goes on the top right-hand corner.

Footnotes are not used in the manuscripts, but parenthetical statements within text are applied instead and sparingly. Abbreviations should be defined at first mention and thereafter used consistently throughout the article. The standard abbreviations for units of measure must be used in conjunction with numbers.

All studies that involve human subjects should not mention subjects' identifying information (e.g. initials) unless the information is essential for scientific purposes and the patients (or parents or guardians) give written informed consent for publication.

2. Title Page

The title page is the first page of the manuscripts and must contain the following:

- The title of the paper (not more than 150 characters, including spaces between words)
- The full names, institutional addresses, and email addresses for all authors (If authors regard it as essential to indicate that two or more co-authors are equal in status, they may be identified by an asterisk symbol with the caption "These authors contributed equally to this work" immediately under the address list.)
- The name, surname, full postal address, telephone number, facsimile number, and email address of the corresponding author who will take primary responsibility for communication with AAP.

- Conflict of interest statement (If there are no conflicts of interest for any author, the following statement should be inserted: "The authors declare that they have no conflicts of interest with the contents of this article.")

3. Abstract

A structured form of abstract is used in all Original Article manuscripts and must include the following separate sections:

- *Background: The main context of the study*
- *Objective: The main purpose of the study*
- *Materials and Methods: How the study was performed*
- *Results: The main findings*
- *Conclusions: Brief summary and potential implications*
- *Keywords: 3 – 5 words or phrases (listed in alphabetical order) representing the main content of the article*

4. Introduction

The Introduction section should clearly explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

5. Materials and Methods

The Materials and Methods section must be described in sufficient detail to allow the experiments or data collection to be reproduced by others. Common routine methods that have been published in detail elsewhere should not be described in detail. They need only be described in outline with an appropriate reference to a full description. Authors should provide the names of the manufacturers and their locations for any specifically named medical equipment and instruments, and all chemicals and drugs should be identified by their systematic and pharmaceutical names, and by their trivial and trade names if relevant, respectively. Calculations and the statistical methods employed must be described in this section.

All studies involving animal or human subjects must abide by the rules of the appropriate Internal Review Board and the tenets of the recently revised Helsinki protocol. Hence, the manuscripts must include the name of the ethics committee that approved the study and the committee's reference number if appropriate.

6. Results

The Results section should concisely describe the findings of the study including, if appropriate, results of statistical analysis which must be presented either in the text or as

tables and figures. It should follow a logical sequence. However, the description of results should not simply repeat the data that appear in tables and figures and, likewise, the same data should not be displayed in both tables and figures. Any chemical equations, structural formulas or mathematical equations should be placed between successive lines of text. The authors do not discuss the results or draw any conclusions in this section.

7. Discussion

The Discussion section should focus on the interpretation and the significance of the findings against the background of existing knowledge. The discussion should not repeat information in the results. The authors will clearly identify any aspects that are novel. In addition, there is the relation between the results and other work in the area.

8. Conclusions

The Conclusions section should state clearly the main summaries and provide an explanation of the importance and relevance of the study reported. The author will also describe some indication of the direction future research should take.

9. Acknowledgements

The Acknowledgements section should be any brief notes of thanks to the following:

- *Funding sources*
- *A person who provided purely technical help or writing assistance*
- *A department chair who provided only general support*
- *Sources of material (e.g. novel drugs) not available commercially*

Thanks to anonymous reviewers are not allowed. If you do not have anyone to acknowledge, please write “Not applicable” in this section.

10. References

The Vancouver system of referencing should be used in the manuscripts. References should be cited numerically in the order they appear in the text. The authors should identify references in text, tables, and legends by Arabic numerals in parentheses or as superscripts. Please give names of all authors and editors. The references should be numbered and listed in order of appearance in the text. The names of all authors are cited when there are six or fewer. When there are seven or more, only the first three followed by “et al.” should be given. The names of journals should be abbreviated in the style

used in Index Medicus (see examples below). Reference to unpublished data and personal communications should not appear in the list but should be cited in the text only (e.g. A Smith, unpubl. Data, 2000).

- *Journal article*
  1. Sibai BM. Magnesium sulfate is the ideal anticonvulsant in preeclampsia – eclampsia. Am J Obstet Gynecol 1990; 162: 1141 – 5.
- *Books*
  2. Remington JS, Swartz MN. Current Topics in Infectious Diseases, Vol 21. Boston: Blackwell Science Publication, 2001.
- *Chapter in a book*
  3. Cunningham FG, Hauth JC, Leveno KJ, Gilstrap L III, Bloom SL, Wenstrom KD. Hypertensive disorders in pregnancy. In: Cunningham FG, Hauth JC, Leveno KJ, Gilstrap L III, Brom SL, Wenstrom KD, eds. Williams Obstetrics, 22nd ed. New York: McGraw-Hill, 2005: 761 – 808.

11. Tables

The tables should be self-contained and complement, but without duplication, information contained in the text. They should be numbered consecutively in Arabic numerals (Table 1, Table 2, etc.). Each table should be presented on a separate page with a comprehensive but concise legend above the table. The tables should be double-spaced and vertical lines should not be used to separate the columns. The column headings should be brief, with units of measurement in parentheses. All abbreviations should be defined in footnotes. The tables and their legends and footnotes should be understandable without reference to the text. The authors should ensure that the data in the tables are consistent with those cited in the relevant places in the text, totals add up correctly, and percentages have been calculated correctly.

12. Figure Legends

The legends should be self-explanatory and typed on a separate page titled “Figure Legends”. They should incorporate definitions of any symbols used and all abbreviations and units of measurement should be explained so that the figures and their legends are understandable without reference to the text.

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14. Components

14.1. Letters to the Editor

The Letter to the Editor manuscripts consist of the following order:

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- *Main Text*
- *References*
- *Table (if needed)*
- *Figure Legend (if needed)*
- *Figure (if needed)*

14.2. Original Articles

The Original Article manuscripts consist of the following order:

- *Title Page*
- *Structured Abstract*
- *Introduction*
- *Materials and Methods*
- *Results*
- *Discussion*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

14.3. Review Articles

The Review Article manuscripts consist of the following order:

- *Title Page*
- *Unstructured Abstract*
- *Introduction*

- *Main Text*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

14.4. Case Reports

The Case Report manuscripts consist of the following order:

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- *Unstructured Abstract*
- *Introduction*
- *Case Description*
- *Discussion*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

14.5. Case Illustrations

The Case Illustration manuscripts consist of the following order:

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- *Clinical Presentation or Description*
- *Laboratory Investigations*
- *Discussion*
- *Final Diagnosis*
- *Multiple Choice Questions (MCQs)*
- *Take-Home Messages (Learning Points)*
- *Acknowledgements*
- *References*
- *Correct Answers to MCQs*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

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- *Introduction*
- *Main text*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

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