Journal of Institute of Medicine Nepal
Institute of Medicine, Kathmandu, Nepal

OPEN ACCESS

Original Article

JIOM Nepal. 2024 Aug;46(2):55-60.

Histopathological Study of Whipple's Pancreaticoduodenectomy Specimens at Tertiary Care Center

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ABSTRACT

Introduction

Whipple's pancreaticoduodenectomy has become a widely used resection procedure for pancreatic head, periampullary, ampullary, and biliary tumors. This study was conducted to analyze the histopathological features of these tumors in pancreaticoduodenectomy specimen.

Methods

A descriptive study was carried out in the Pathology Department of Kathmandu Medical College Teaching Hospital. Pancreaticoduodenectomy specimens received were assessed for tumor location, histopathologic categorization, grading, lymphovascular and perineural invasion, margin status, and lymph node status. AJCC TNM staging was done.

Results

Out of 41 Whipple's pancreaticoduodenectomy cases, 35 (85.4%) were malignant and 6 (14.6%) were benign. The patients' ages ranged from 30 to 84 years, with a mean age of 58.3 years and a male to female ratio of 1.2:1. Adenocarcinoma was the most common malignant lesion (73.2%; n=30) frequently found in the intra-ampullary and periampullary regions (31.4%; n=11). The intestinal type of adenocarcinoma was the most common (42.8%; n=15), followed by the pancreaticobiliary type (34.3%; n=12). Most tumors were moderately differentiated (74.3%; n=26). Perineural invasion was frequently seen in intra-ampullary and periampullary carcinoma (81.8%; n=9). Lymphovascular invasion was frequently seen in intra-ampullary and periampullary carcinoma (81.8%; n=9). Most tumors were in the T3 stage (42.9%; n=15), and overall nodal metastasis (N1 and N2) was seen in 57.1% (n=20).

Conclusion

Adenocarcinoma was the commonest diagsosis in pancreaticoduodenectomy specimens of the intra-ampullary and periampullary region. Malignant lesions were more frequent than benign lesion in our study.

Keywords

Adenocarcinoma; lymphovascular invasion; perineural invasion; whipple's pancreaticoduodenectomy

DOI

10.59779/jiomnepal.1293

Submitted

Mar 8, 2024

Accepted

Jul 11, 2024

INTRODUCTION

Italian surgeon Alessandro Codivilla performed the first pancreaticoduodenectomy (PD) for a pancreatic head lesion.[1] Allan Whipple, who popularized the operation now named after him, documented 37 PDs and developed modifications that evolved the procedure from two stages to one by the early 1940s, improving surgical mortality.[2]

This procedure has increasingly been used now a days for periampullary carcinoma, ampullary carcinoma, duodenal carcinoma, tumor of common bile duct and pancreatic tumors. PD is also performed for some benign lesions because they can mimic malignant ones or cause obstructive symptoms.[2] Due to the complexity of the specimen, pathological assessment requires special attention to evaluate many prognostically important factors. These factors include tumor location, extension, size, surgical margin status, lymphovascular invasion (LVI), perineural invasion (PNI), and lymph node status.[3]

The aim of this study is to analyse the histopathological findings in Whipple's PD specimens on the basis of American Joint Committee on Cancer (AJCC) guidelines.[4]

METHODS

This is a descriptive cross-sectional study done at Pathology Department of Kathmandu Medical College Public Limited, Sinamangal, Nepal from January 2023 to October 2023. Ethical approval was taken from the Institutional review committee of Kathmandu Medical college teaching hospital (Reference number:04122022/06). All Whipple's PD specimens received at Pathology Department of Kathmandu Medical College and Public Limited, Sinamangal were included this study. The specimens with prior history of neoadjuvant therapy were excluded from the study. Informed written consent was taken. Relevant demographic data was obtained from requisition form provided with the specimens. The PD specimens received in department of pathology were fixed in 10% formalin and grossed. Strict criteria for the location of tumor as ampullary, periampullary duodenal, intra-ampullary and periampullary, common bile duct was applied.[5,6]

1. Tumors with epicentre in the ampulla were categorised as ampullary carcinomas.

2. Tumors growing on the duodenal surface of papillae as periampullary duodenal carcinomas.

3. Tumors with both intra-ampullary and periampullary growth pattern were categorised as intra-ampullary and periampullary regions (mixed type).

4. Tumors involving the circumference of the common bile duct were categorised as common bile duct tumours.

The tissue was processed in automated histokinette, sectioned and stained with Hematoxylin & eosin (H&E). The slides prepared were examined . Tumor origin, tumor typing, tumor grading, LVI and PNI, margin and lymph node status were assessed. Tumor, node and metastasis (TNM) staging of the tumor was done based on AJCC TNM classification.[4]

The data was entered and analyzed using IBM SPSS version 22.0. Descriptive statistics (frequency, percentage and mean) were used to explain the characteristics of different variables measured in the study.

RESULTS

From January 2023 to October 2023, a total of 41 Whipple's PD were carried out. Among these, 23 (56.1%) were males and 18 (43.9%) were females, with a male to female ratio of 1.2:1. The age ranged from 30 to 84 years, with a mean age of 58.3years. Most common age group was 61-70 years comprises of 13 cases (31.7%) (Table1).

Malignant lesion was seen in 35 cases (85.4%) where as benign lesion was seen in 6 cases(14.6%) (Table 2). Adenocarcinoma was most malignant lesion seen in 73.2% (n=30) and chronic pancreatitis was a common benign lesion seen in 9.8% (n=4) (Table 2).

Table 1. Age distribution of patients (n=41)

Age group (years)	Number (%)
<30	1 (2.5)
31-40	6 (14.6)
41-50	6 (14.6)
51-60	7 (17.1)
61-70	13 (31.7)
71-80	6 (14.6)
>80	2 (4.9)

Table 2. Histopathologic diagnosis of lesion

Histologic type	Number (%)
Malignant	
Adenocarcinoma	35 (85.4)
IPMN with associated invasive carcinoma	30 (73.2)
PNET	3 (7.3)
	2 (4.9)
Benign	6 (14.6)
Chronic pancreatitis	4 (9.8)
Pulse granuloma	1 (2.4)
Serous cystadenoma	1 (2.4)

Table 3. Site and size wise distribution of malignant tumor (n=35)

Tumor site	Number (%)	Mean tumor size (cm)	Range (cm)
Intra-ampullary and periampullary	11 (31.4)	3.1	1.5-6.1
Pancreatic head	8 (22.9)	3.7	2.5-4.8
Distal common bile duct	7 (20.0)	2.8	2.0-4.0
Intra-ampullary	5 (14.2)	1.9	1.2-2.4
Periampullary duodenal	3 (8.6)	2.6	2.4-3.0
Pancreatic body	1 (2.9)	3.6	3.60

Malignant lesion was commonly seen in intra-ampullary and periampullary region (31.4%; n=11) followed by pancreatic head (22.9%; n=8) (Table 3).

The largest mean tumor size found in pancreatic head was 3.7 cm (range 2.5-4.8) followed by pancreatic body (3.6 cm) (Table 3).

Intestinal type of Adenocarcinoma was common histologic type seen in 42.8% (n=15) followed by Pancraticobiliary type seen in 34.3% of cases (n=12). The other malignant tumors were Ductal adenocarcinoma, not otherwise specified (NOS) (8.6%); Intraductal papillary mucinous neoplasm(IPMN) with invasive carcinoma (8.6%) and Pancreatic neuroendocrine tumor (PNET's) (5.7%) (Table 4).

The common histologic grade was moderately differentiated (74.3%; n=26) (Table 4). PNI was commonly seen in Intra-ampullary and periampullary

Table 4. Histopathological features of malignant tumor (n=35)

Tumor stage	Ampulla	Periampullary duodenal	Intra-ampullary and periampullary	Distal common bile duct	Pancreatic head	Pancreatic body	Total
Histologic type							
Adenocarcinoma, Intestinal type	4(11.4%)	1(2.8%)	7(20%)	2(5.7%)	1(2.8%)	0	15(42.8%)
Adenocarcinoma, pancreaticobiliary type	1(2.8%)	2(5.7%)	4(11.4%)	5(14.2%)	0	0	12(34.3%)
Neuroendocrine tumor	0	0	0	0	1(2.8%)	1(2.8%)	2(5.7%)
Ductal adenocarcinoma NOS	0	0	0	0	3(8.6%)	0	3(8.6%)
IPMN with associated invasive carcinoma	0	0	0	0	3(8.6%)	0	3(8.6%)
Histologic grade							
Well differentiated	1(2.8%)	1(2.8%)	1(2.8%)	2(5.7%)	2(5.7%)	1(2.8%)	8(22.9%)
Moderately differentiated	4(11.4%)	2(5.7%)	10(28.6%)	4(11.4%)	6(17.1%)	0	26(74.3%)
Poorly differentiated	0	0	0	1(2.8%)	0	0	1(2.8%)
PNI							
Present	2(40%)	2(66.6%)	9(81.8%)	5(71.4%)	6(75%)	0	24(68.5%)
Absent	3(60%)	1(33.3%)	2(18.2%)	2(28.6%)	2(25%)	1(100%)	11(31.5%)
LVI							
Present	2(40%)	2(66.6%)	9(81.8%)	5(71.4%)	6(75%)	0	24(68.5%)
Absent	3(60%)	1(33.3%)	2(18.2%)	2(28.6%)	2(25%)	1(100%)	11(31.5%)
Total lymphnode dissected							
Range	8-14	13-31	4-19	3-17	7-28	14	-
Mean	10.8	19.3	14.1	10.5	14.6	14	
Total case with involved lymphnodes	2/5 (40%)	1/3 (33.3%)	9/11 (81.8%)	3/7 (42.8%)	5/8 (62.5%)	0/1	20/35 (57.1%)
Margin positivity	0	0	1(2.8%) (SMA)	1(2.8%) (CBD)	2(5.7%) (Posterior pancreatic)	0	-

Table 5. Pathological tumor stage of malignant tumor (n=35)

Tumor stage	Ampulla	Periampullary duodenal	Intra-ampullary and periampullary	Distal common bile duct	Pancreatic head	Pancreatic body	Total
T1	2(5.7%)	0	4(11.4%)	2(5.7%)	2(5.7%)	0	10(28.6%)
T2	2(5.7%	1(2.8%)	1(2.8%)	1(2.8%)	3(8.6%)	1(2.8%)	9(25.7%)
T3	1(2.8%)	2(5.7%)	6(17.1%)	3(8.6%)	3(8.6%)	0	15(42.9%)
T4	0	0	0	1(2.8%)	0	0	1(2.8%)
Total	5(14.2%)	3(8.6%)	11(31.4%)	7(20%)	8(22.9%)	1(2.8%)	35(100%)

Table 6. Pathological nodal stage of malignant tumor (n=35)

Nodal stage	Ampulla	Periampullary duodenal	Intra-ampullary and periampullary	Distal common bile duct	Pancreatic head	Pancreatic body	Total
N0	3(8.6%)	2(5.7%)	2(5.7%)	4(11.4%)	3(8.6%)	1(2.8%)	15(42.9%)
N1	1(2.8%)	1(2.8%)	6(17.1%)	2(5.7%)	2(5.7%)	0	12(34.2%)
N2	1(2.8%)	0	3(8.6%)	1(2.8%)	3(8.6%)	0	8(22.9%)
Total	5(14.2%)	3(8.6%)	11(31.4%)	7(20%)	8(22.9%)	1(2.8%)	35(100%)

carcinoma (81.8%; n=9). LVI was commonly seen in intra-ampullary and periampullary carcinoma (81.8%; n=9) followed by pancreatic head carcinoma (75%; n=6). Margin positivity was commonly seen in pancreatic head carcinoma (5.7%; n=2) (Table 4). Most of the tumors were in the T3 stage (42.9%; n=15) (Table 5).

The overall nodal metastasis (combined N1 and N2) were seen in 20 cases (57.1%) (Table 6).

DISCUSSION

PD is fairly complex procedure and studies have shown even after advances in surgery in PD procedure, it continues to have significant morbidity and mortality but still plays an integral part in the management of patient. Surgical resection at present offers the only chance of cure for periampullary, pancreatic and duodenal cancers. PD specimens are a challenge for surgical pathologists because of the relative rarity of these specimens as well as the anatomic complexity.[7-9] Because of presence of complex architecture in the ampulla characterized by duodenal and ductal type of epithelium and presence of branched submucosal glands, in-situ component is difficult to differentiate from an invasive carcinoma in some cases.[10]

Among 41 patient underwent PD, 23(56.1%) were male and 18(43.9%) were female with a ratio of 1.2:1. Other studies done at Nepal and India also found male predominance and is comparable to our study.[5,10,11] The mean age was 58.37 years in our study with a age range of 30-84 years. These findings corresponds with a similar studies done at Iran, Nepal and sudan.[4,10,12] In our study, most of the cases of PD was done in a age group of 61-70 years comprises of 13 cases (31.7%). This result was similar to the previous study done by Dhakhwa et al where they found 15(42.8%) of cases of PD done at 61-70 years.[11] However the study done by Ashima Nagesh Amin et al found majority of patient in a age range of 51-60 years.[5]

In the current study, 14.6% of cases were benign and chronic pancreatitis was most common among benign lesion (9.8%). The literature reports that 4-14% of the lesions identified at PD are benign and chronic pancreatitis as a commonest one.[3,10–13] However, Yeo et al. reported 32% of benign lesions including chronic pancreatitis as a commonest one seen in 11% in their study. This difference might be because of large number of cases (650 cases) analysed in their study as compared to ours (41cases).[1] We identified one case of pulse granuloma characterized by a hyaline ring, multinucleated giant cells, and dense inflammation found in the duodenum and extending into the head of the pancreas. Pulse granuloma occurs as a reaction to vegetable material and is usually observed in the oral cavity, with rare occurrences in the gastrointestinal tract. It can mimic a mass lesion in computed tomography scans.[14]

We found 35 cases (85.4%) of malignant tumor and the commonest site was intra-ampullary and periampullary comprises of 11 cases (31.4%) followed by pancreatic head tumor comprises of 8 cases (22.9%). The largest mean tumor size we found at pancreatic head was 3.78 cm (range 2.50-4.80 cm) and the smallest mean tumor size at intra-

ampullary region was 1.92 cm (range1.2-2.4 cm). In concordance to our study, malignancy accounted for 86%-96% of cases in various studies done at different centers of Nepal, India and Iran.[3,5,10,11]Similar to our findings, intra-ampullary and periampullary region as a commonest site in various studies.[1,5,11] However in contrast to our study Karki et al, Duffy et al and Talamani et al reported ampullary region as a commonest site. In our study, we found 5(14.2%) tumors in intra-ampullary region. This variation in result might be due to the fact that we adhere to the strict diagnostic criteria proposed by Howe JR et al for the diagnosis of intra-ampullary carcinoma.[15]

Adenocarcinoma was a commonest malignant tumor we reported in 30 cases (73.2%) which was similar to the other studies.[5,11]PNETs, or islet cell tumors, are rare and make up 1%-4% of all pancreatic tumors. Most of them (90%) are not cancerous and are usually found in the body and tail of the pancreas.[16] We found 2 cases (4.9%) of PNET, one in the head and one in the body of the pancreas. Since Ohashi et al. first described IPMN of the pancreas in 1982, it has been diagnosed more often and now comprises of 17-25% of pancreatic tumors removed by surgery. IPMN generally has a good prognosis, but if it includes an invasive component, the prognosis is much worse. About 30% of resected IPMNs have invasive cancer.[17]In our study we found 3 cases (7.3%) of IPMN with associated invasive carcinoma.

Histopathologically, ampullary/periampullary carcinoma can be classified into intestinal type, pancreaticobiliary type, mixed type, and undifferentiated type. This classification is important because the intestinal type has a better prognosis than the pancreaticobiliary type.[11] In our study, we found that the majority of cases (42.8%) were of intestinal type . Similar results were reported by other studies done at Nepal and India.[5,11] The histopathologic grade is important for prognosis. High-grade carcinomas typically have a less favorable outcome.[11]In this study, moderately differentiated adenocarcinomas were the most common comprises of 74.3% of cases. This result was comparable to the other studies done at Nepal and Sudan.[10,12]

PNI, LVI and regional lymph node metastasis are critical predictors of recurrence risk and important prognostic factors. LVI and PNI indicates a higher likelihood of tumor spread to nearby lymph nodes and beyond. In cases where LVI and PNI were absent, patients undergoing Whipple resection showed 5-year survival rates of 77% for all malignancies and 71% for pancreatic adenocarcinoma. These factors, easily identified on H&E sections, significantly predict survival following pancreatic resection for malignancies.[10,18,19]We found PNI and LVI in most of the cases with Intra-ampullary and periampullary carcinoma (81 .8%)followed by pancreatic head carcinoma (75%). In contrast to our study, PNI and LVI is frequently observed in pancreatic head carcinoma in other studies.[1,10] This difference in findings could be due to the larger number of cases included in their study compared to ours. In our study, the mean number of lymph nodes retrieved was 13.5. When considering lymph node involvement by malignant tumors, 20 cases (57.14%) showed lymph node metastasis. This rate is notably higher compared to studies by Ibrahim et al. (10%) and Allema JH et al. (40%).[2,20]Similar to our study, Dhakhwa et al found nodal metastasis in 54.8% of cases.[11]

A positive surgical resection margin is generally associated with a poorer prognosis. There are ongoing debates and controversies regarding the significance of positive resected margins in terms of survival benefit. According to College of American Pathologist (CAP) guidelines from November, 2021, the presence of tumor at or within 1mm of the resection margin is considered a positive margin.[4] Not all margins may affect patient survival equally. Delpero et al. found that a positive margin at the Superior Mesenteric Artery (SMA) or Superior Mesenteric Vein (SMV) significantly impacted progression-free survival, whereas a positive posterior margin did not have the same impact.[21] In our study, we found one case with a positive Superior Mesenteric Artery (SMA) margin (2.8%) in intra-ampullary and periampullary carcinoma, one case with a positive Common Bile Duct (CBD) margin (2.8%) in distal CBD carcinoma, and 2 cases with positive posterior pancreatic margins (5.7%) in pancreatic head carcinoma.

Our study showed that most of the tumors were in the T3 stage, comprising 15 cases (42.9%). In contrast, a five-year study conducted in India found that the T2 stage was the most common (57.1%).[5]Karki et al. also found the T2 stage to be the most common in their study.[10] Similar to our findings, a study of 51 cases over a five-year period in Iran reported most of their cases in the T3 stage.[3] The overall nodal metastasis (combined N1 and N2) were seen in 20 cases (57.1%) in our study. The incidence of nodal metastasis ranges from 29 to 52% in different studies.[20,22]

The limitation of this study was that the samples were collected from a single tertiary center, limiting the generalizability of the findings to the entire Nepalese population. Therefore, we recommend conducting similar studies across multiple centers with larger sample sizes.

CONCLUSION

Adenocarcinoma was the most common diagnosis in pancreaticoduodenectomy specimens of the intra-ampullary and periampullary region. Malignant

lesions were more frequent than benign lesion in our study. Perineural invasion as well as lymphovascular invasion was frequently seen in intra-ampullary and periampullary carcinoma.

FINANCIAL SUPPORT

The author(s) did not receive any financial support for the research and/or publication of this article.

CONFLICT OF INTEREST

The author(s) declare that they do not have any conflicts of interest with respect to the research, authorship, and/or publication of this article.

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