

Histopathological Findings of Pancreaticoduodenectomy Specimens in a Tertiary Care Hospital in Nepal

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ABSTRACT

Introduction

Among the gastrointestinal malignancies, 5% of the tumors comprise peri-ampullary carcinomas. Adenocarcinoma is the commonest malignancy in the peri-ampullary region. The important histopathological prognostic factors are tumor size, location, extension, resected marginal status, lymphovascular (LVI) and perineural invasion (PNI) and lymph nodal status. This study was conducted to analyze the lesions and to describe the associated histopathological parameters.

Methods

This study was carried out in the Department of Pathology, TUTH, Kathmandu, includes pancreatico-duodenectomy specimens submitted from April 2016 to September 2020. The related details were obtained from the archives of reports in the Department. Statistical analysis was performed using IBM SPSS v26.

Results

Among 111 specimens, 100 (90%) malignant lesions, 10 (9.1%) benign lesions and 1 (0.9%) pre-malignant lesions were seen. M:F ratio was 1.2:1 with mean age 55.5 years. Ampulla was the most common site of malignancy (61%) and adenocarcinoma was the commonest histological type. Chronic pancreatitis (4.5%) accounted for most of the benign lesions. Ampullary and pancreatic malignancies were detected in T2 stage, 55.7% and 77.8% respectively. LVI was seen in 61% and PNI in 72% of pancreatic malignancies. Positive resected margin was seen in 6% of malignancies. SMA was the most common positive margin.

Conclusion

Pancreatico-duodenectomy was performed mostly for adenocarcinomas of ampulla. Pancreatic tumors were common in the older age group and they presented with LVI and PNI and at a higher T and N status as compared to ampullary or duodenal tumors.

Keywords

Lymphovascular invasion, margins, perineural invasion, pancreatico-duodenectomy specimen

INTRODUCTION

In 1935, Allan Whipple first described this operative procedure for periampullary carcinomas.¹ Later the indications were extended to pancreatoduodenal resection to include tumors of the pancreas.² Whipple procedure is mostly performed for tumors of ampulla, duodenum, distal bile duct and pancreas. Among the gastrointestinal malignancies, 5% of the tumors comprise periampullary carcinomas.³ The most common tumor in the ampullary region is adenocarcinoma, approximately 80%.³ Pancreatic cancers are the 12th commonest cancer in the world.⁴ The ductal adenocarcinoma of the head of pancreas has a poor prognosis.⁵ The only curative treatment for such tumors in these areas is surgical resection.

Because of the complexity of many structures in this location even a benign lesion can lead to obstructive symptoms. Pancreatoduodenectomy has been performed for many such benign conditions that mimic malignancy.³ Histopathology is the gold standard to diagnose benign and malignant lesions.

The proper reporting of these resection specimens starts with appropriate handling of the surgical pathological specimens in the grossing room, wherein, correct anatomical orientation of the specimen along with recognition of the surgical margins is required. Special attention should be given to the pathological assessment of these resection specimens to accurately report all factors that play an important role in the prognosis of the individual. The factors included are tumor size, location, extension, resected marginal status, lymphovascular and perineural invasion and lymphnodal status.⁶

This was a retrospective study conducted to comprehensively analyze the various lesions, both benign and malignant, and to describe the histopathological parameters associated with prognosis of the tumor.

METHODS

This was a retrospective study which included pancreatoduodenectomy specimens received

from April 2016 to September 2020 in the Department of Pathology, TUTH, Kathmandu, Nepal. The pertinent details related to the pathological prognostic factors like tumor size, location, extension, resected marginal status, lymphovascular (LVI) and perineural invasion (PNI) and lymph nodal status, were obtained from the archives of reports in the Department. TNM staging was done according to AJCC classification 8th edition. Analysis of data was done using IBM SPSS v26. Pearson's correlation coefficient was used to obtain the p-value.

RESULTS

During the study period from April 2016 to September 2020, 111 cases of pancreatoduodenectomies were received in the Department of Pathology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal. The M:F ratio for pancreatoduodenectomy was 1.2:1 with age ranging from 11-86 years, mean age 55.5 years. Examination of these specimens revealed 100 (90%) malignant lesions, 10 (9.1%) benign lesions and 1 (0.9%) pre-malignant lesion.

Among the 100 malignant lesions, 61 cases were in the ampulla (61%), 18 cases in pancreas (18%), 6 cases in duodenum (6%), 14 cases in distal extrahepatic common bile duct (14%) and 1 in the cystic duct (1%). Most of the malignancies were seen in males, 55%. Ampullary malignancies were frequently seen in 51-60 years of age (Table 1).

Size of the malignant lesions ranged from 0.6-8.5cm. Larger sized lesions were located in the duodenum and pancreas. Relatively smaller sized lesions were noted in the ampulla and CBD (Table 2). However, the difference in the size of the tumor according to the location was not statistically significant (p=0.06).

From the total of 100 malignant lesions, adenocarcinomas were 90% (90 cases), which were mostly located in the ampulla (65.5% of adenocarcinomas, 59/90 cases). Other malignant tumors were solid pseudopapillary neoplasm (4%), gastrointestinal stromal tumor (3%), G1 panNET (2%) and intraductal papillary mucinous neoplasm with invasion (1%). Most of the ampullary and

Table 1. Age and sex distribution of malignant lesions in pancreatoduodenectomy specimens

Site	Age group (years)								Sex	
	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	Male	Female
Ampulla	0	0	9	10	22	15	4	1	34	27
Duodenum	0	0	0	2	2	2	0	0	3	3
Pancreas	1	2	2	1	4	4	4	0	11	7
CBD	0	0	0	1	7	2	4	0	6	8
Cystic duct	0	0	0	0	0	0	1	0	1	0
Total	1 (1)	2 (2)	11 (11)	14 (14)	35 (35)	23 (23)	13 (13)	1 (1)	55 (55)	45 (45)

Table 2. Size of malignant lesions according to site distribution

Site	Size (cm)				Total
	1-2	2.1-3	3.1-4	>4	
Ampulla	36	14	5	6	61 (61%)
Duodenum	2	0	0	4	6 (6%)
Pancreas	1	6	7	4	18 (18%)
CBD	12	2	0	0	14 (14%)
Cystic duct	1	0	0	0	1 (1%)
Total	52 (52%)	22 (22%)	12 (12%)	14 (14%)	100 (100%)

pancreatic malignancies were detected in T2 stage, 55.7% and 77.8% respectively. 50% of duodenal malignancies showed LVI and PNI. Perineural invasion was seen in 72% and LVI in 61% of pancreatic malignancies. Six cases had positive resected margins, mostly superior mesenteric

artery (SMA) margin was found to be positive (3 out of 6 cases). Mostly pancreatic tumors had positive margin (Table 3).

LVI and PIN differ according to the location of the tumor ($p=0.04$ and 0.01 respectively). They are

Table 3. Features of malignant lesions in the pancreatico-duodenectomy specimen

Features	Site				
	Ampulla	Duodenum	Pancreas	CBD	Cystic duct
Peak age group (years)	51-60	41-70	51-80	51-60	NA
Male:Female ratio	1.3:1	1:1	1.5:1	1:1.3	NA
Mean tumor size (cm)	2.3	5.75	3.85	1.7	1.5
Histopathological type					
1. Adenocarcinoma (n=87)					
i. VLD adenoca	25	1	3	2	0
ii. MD adenoca	31	1	10	9	1
iii. PD adenoca	2	1	0	1	0
2. Mucinous adenocarcinoma (n=2)	1	1	0	0	0
3. Adenosquamous carcinoma (n=1)	0	0	0	1	0
4. Solid pseudopapillary neoplasm (n=4)	0	0	4	0	0
5. GIST (n=3)	2	1	0	0	0
6. NET, G1 (n=2)	0	1	1	0	0
7. IDPMN with invasion (n=1)	0	0	0	1	0
LVI seen (n=49)	30 (49.1%)	3 (50%)	11 (61%)	5 (35.7%)	0
PNI seen (n=47)	22 (36%)	3 (50%)	13 (72%)	8 (57.1%)	1 (100%)
Tumor stage					
T1 (n=4)	4 (6.6%)	0	0	0	0
T2 (n=55)	34 (55.7%)	2 (33.3%)	14 (77.8%)	5 (35.7%)	0
T3 (n=39)	23 (37.7%)	2 (33.3%)	4 (22.2%)	9 (64.3%)	1 (100%)
T4 (n=2)	0	2 (33.3%)	0	0	0
Lymphnode status					
N0 (n=63)	40 (65.6%)	4 (66.7%)	8 (44.4%)	10 (71.4%)	1
N1 (n=29)	17 (27.8%)	0	8 (44.4%)	4 (28.6%)	0
N2 (N=8)	4 (6.6%)	2 (33.3%)	2 (11.2%)	0	0
Positive margin (n=6)	1 (SMA)	0	3 (2 SMA and 1 anterior)	1 (resected CBD margin)	1 (resected cystic duct margin)

more common in the pancreatic tumors. Higher T stage and positive N status was seen in pancreatic tumors ($p=0.05$). Higher grades of adenocarcinomas were associated with a higher T stage and positive N (nodal) status ($p=0.01$ and 0.05 respectively). PNI and LVI were associated with high T stage and positive nodal status at presentation (p -value 0.05 and 0.01 respectively).

Out of ten benign lesions found in pancreatoduodenectomy specimen, five were chronic pancreatitis (50%), two adenomyomas of ampulla (20%), one case of adenoma, gastric type of ampulla (10%) and one case of serous cystadenoma of pancreas (10%) and one case of xanthogranulomatous pancreatitis (10%). Chronic pancreatitis accounted for 4.5% of all pancreatoduodenectomies. One case of pre-malignant lesion was an intraepithelial neoplasia in the bile duct.

DISCUSSION

Pancreatoduodenectomy is performed for all tumors of ampulla, duodenum, pancreas and common bile duct. Dual type of epithelium, consisting of duodenal and ductal type, is seen in the ampulla. Complex and branched submucosal glands are present here. Due to its complex architecture, in-situ component may be difficult to distinguish from an invasive carcinoma in some cases. In such instances, features like lobular glandular architecture, rounded glands and no stromal response help in making a former diagnosis.

In this study, 9.1% of total pancreatoduodenectomy specimens had a benign lesion. Benign lesions in pancreatoduodenectomies have been observed to range from 7-15%.⁷⁻⁹ A study carried out over a period of six years at The Johns Hopkins Hospital which included 650 pancreatoduodenectomies, showed 32% benign lesions, in which chronic pancreatitis accounted for 11%.¹⁰ Chronic pancreatitis was 4.5% of all cases in our study.

With improved outcome of Whipple procedure, it is said to be associated with 1-2% mortality when performed in high volume centers.¹¹ Despite the use of imaging studies, tissue typing and serological tests, the percentage of benign finding showed an increasing trend in Whipple procedure over recent years in a study carried out in Atlanta, Emory University School of Medicine.¹² Their study included 878 Whipple procedures performed between January 1998 and December 2011.

In this study, the overall M:F ratio for pancreatoduodenectomy was 1.2:1. A study from a tertiary care centre in North India reported M:F= 2.3:1. Their study included 786 pancreatoduodenectomies which were received over a period of 15 years.¹³ However, a two year study in India reported a M:

F ratio 1:1.3 This two year study had 36 cases. Equal number of cases in both sexes were seen in duodenal tumors in our study.

Our study showed an age range from 11-86 years with mean age 55.5 years and mean size of tumor 2.3cm. In a five year study carried out in Iran which included 51 samples, age ranged from 18-82 years with average age 57 years and mean size 2.8cm.⁷ Our study showed that among the malignant lesions, peak of adenocarcinomas were seen in the fifth to sixth decade of life, while, the peak of solid pseudopapillary neoplasm was seen in the second decade.

Malignant lesions accounted for 90% of all resected specimens and 61% of them were located in the ampulla in our study. Malignancy accounted for 86.3% of cases among which 61.4% of the lesions were located in the ampulla in a similar study carried out at Taleghani General Hospital, Iran.⁷ The youngest age at which ampullary malignancy was seen in our study was 32 years. The youngest age mentioned in a 140 month study in Memorial Sloan-Kettering Cancer Center enrolling 163 cases of carcinoma of the ampulla of Vater was 28.3 years with a history of familial adenomatosis syndrome.¹⁴

Ninety percent of malignant lesions were adenocarcinomas and 65.5% of these adenocarcinomas were located in the ampulla in our study. This is similar to another study carried out in Asia where they reported 70% of ampullary adenocarcinomas.³ In contrast to these studies, studies carried out in the western world reported pancreatic adenocarcinomas as the commonest site of tumor in pancreatoduodenectomy specimens.^{15,16}

Moderately differentiated adenocarcinomas predominated in this study. Among 30 cases included in a study carried out in Madurai Medical College, India, well and moderately differentiated carcinomas were 38% and 62% respectively.³ In a five year study conducted in India, well differentiated adenocarcinomas were the commonest subtypes of tumors of pancreas (57.1%) and ampulla (87.5%).¹⁷ Histopathologic grade is associated with prognostic significance. High grade carcinomas have relatively less favorable prognosis.¹⁸ Poorly differentiated adenocarcinomas were significantly associated with higher T stage and positive nodal status in our study.

Our study showed that most of the ampullary and pancreatic tumors were in T2 stage whereas a five year study conducted in India showed that ampullary tumors presented commonly in T2 stage (57.1%) and pancreatic tumors in T3 stage (40%).¹⁷ A study of 51 cases over a five year period in Iran reported most of their cases in T3 stage.⁷ Fifty percent of their cases were in stage T3 indicating a diagnosis being made at late stage of the disease.

Nodal metastasis was seen in 34.4% of ampullary, 44.4% of pancreatic tumors and 28.6% of CBD tumors in this study. Nodal metastasis was seen in 13% of CBD tumors and 28% of ampullary and pancreatic tumors in a study carried out in Florida which involved 348 resected specimens.¹⁹ A study carried out in the Netherlands including 67 patients undergoing pancreatico-duodenectomy for ampullary carcinoma, reported nodal metastasis in 52% of the cases.²⁰ The higher TN status were significantly associated with pancreatic tumors.

Perineural invasion (PNI), lymphovascular invasion (LVI), loco regional lymph node metastasis, pathologic stage of tumor and microscopic assessment of margins are important predictive factors for risk of recurrence and important prognostic factors.^{21,22} Lymphovascular or perineural tumor infiltration is indicative of risk of regional tumor spread along with metastasis to regional lymph node. All cases showing lymphovascular invasions had a positive nodal status in this study. Perineural invasions were commonly seen in pancreatic and CBD tumors as compared to ampullary tumors. Another study showed equal numbers of LVI and PNI in both ampullary and pancreatic tumors.⁷ Presence of perineural invasion and lymphovascular invasion was associated with higher TN stage in our study.

Positive surgical resection margin is associated with poor prognosis. There are debates and controversies regarding positive resected margin and their significance in survival benefit. Earlier, according to American pathologists, microscopically negative margins meant absence of tumor cells at the inked margin whereas negative margin meant absence of tumor cells within 1 mm of surgically resected margin for European authors.^{21,22} However, now according to CAP guidelines, 13 June 2017, presence of tumor at or within 1mm of resection margin is considered a positive margin.¹⁸

Significantly reduced survival is reported in patients with microscopic superior mesenteric artery (SMA)/ superior mesenteric vein (SMV) margin involvement as compared to margin negative resections.²² Importance of complete resection with microscopically negative resection margins (Ro resection) for cure in patients with resectable pancreatic cancers has been emphasized in different studies.²² Six percentage of pancreaticoduodenectomy specimens resected for malignancy had positive margin in our study. Fifty percentage of those positive resection margins were seen in pancreatic cancers and they were SMA margin. In another similar study, 10.3% positive margin was found in Whipple specimens.⁵ In case of pancreatic tumors in the same study, 16.4% had positive margin. They too showed predominantly positive SMV margin.⁵

A population based study carried out in George Washington University Cancer Institute, Washington, states that the incidence of pancreatic endocrine neoplasm (panNET) is less than 3% of all the pancreatic neoplasms.²³ They have also mentioned that ductal carcinoma is more common among the pancreatic neoplasm. In our study also mostly ductal adenocarcinomas of pancreas were seen. Only a single case of G1 pan NET was noted. Younger age incidence for endocrine tumors was associated with MEN syndrome and VHL disease in a study carried out in Sweden.²⁴ Male predominance was seen in their study. Though it is an indolent tumor it has malignant potential. Compared to adenocarcinoma of the pancreas, endocrine tumors have better prognosis.²⁵

Solid pseudopapillary tumor is predominantly a tumor of the young female and middle aged women. A study in India of solid pseudopapillary neoplasm of the pancreas involving 14 cases, reported its prevalence in young females with the median age of 20 years.²⁶ Another study mentioned the median age as 39 years.²⁷ The youngest age at which this tumor was seen in this study was a 11year old male. Solid pseudopapillary tumor is a cystic and solid neoplasm that mostly involves the head and tail of the pancreas. This is a tumor of low malignant potential with frequent metastasis to the liver. Surgery is the treatment of choice for localized tumors and for metastatic tumors, aggressive management is required.

Duodenal adenocarcinoma comprises about 1% of all gastrointestinal tumors.⁴ The majority of adenocarcinomas arise in second part. Adenocarcinomas of the first part of duodenum is rare. The adenocarcinoma arising from the second part of duodenum require pancreaticoduodenectomy. The important prognostic factors for these neoplasms include tumor grade, lymphnode and distant metastasis, stage of tumor (T), marginal status, presence of LVI and /or PNI and the overall stage. In our study 4% duodenal adenocarcinomas were found.

Primary cystic duct carcinoma is rare.²⁸⁻³⁰ Cystic duct carcinoma was defined by Farrar in 1951 as (1) growth limited to the cystic duct, (2) absence of neoplasia in the common bile duct, hepatic duct or gallbladder, and (3) histological confirmation of malignant cells in the mass.²⁸ One study conducted for a period of 16 years, found 15 cases of cystic duct carcinoma which accounted for 6.6% of all malignant biliary tumors. A single case of cystic duct carcinoma was reported in this study.

CONCLUSION

This study highlighted that pancreaticoduodenectomy is being performed in our institute mostly for adenocarcinomas of ampulla. Pancreatic

tumors were common in the older age group and they presented with LVI and PNI and at a higher T and N status as compared to ampullary or duodenal tumors.

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CONFLICT OF INTEREST

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