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Original Research Article

Clinicopathological analysis of Whipple's pancreaticoduodenectomy resection specimens- An institutional experience

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Abstract

Background: Whipple's pancreaticoduodenectomy (PD) is performed for various benign and malignant conditions of pancreas, duodenum and its periampullary region. 5% of the gastrointestinal malignancy is constituted by the ampullary and periampullary carcinoma. Histopathological studies helps in diagnosis, grading, staging, nodal status, marginal status, prognosis of the tumor.
Aim: To study the clinicopathological spectrum of Whipple's pancreatico-duodenectomy specimens.
Materials and Methods: This is a retrospective cross-sectional study of 7 years, wherein 20 cases of Whipple's PD were analyzed. Clinical details and gross examination findings were examined in detail and reported as per AJCC 8th edition of CAP protocol.
Results: Of the 20 cases, male to female ratio was 1.5:1, obstructive jaundice was the most common presenting complaint followed by abdominal pain. 8 of the 20 cases underwent pylorus preserving surgery and rest were classical Whipple's surgery. The mean age of the study group was 55.2 years. 19 cases were malignant and one case was benign with periampullary region as the most common site of malignancy (31.5%). 68.8% were diagnosed to have intestinal type of adenocarcinoma and it was the most common histological type. One case was diagnosed as chronic pancreatitis. Lymphovascular invasion was seen in 3 of the 4 cases of pancreatic adenocarcinoma and in one case of periampullary carcinoma. Majority of the tumors were moderately differentiated (56.2%).
Conclusion: Intestinal adenocarcinoma is the most common histological subtype in our study. It is important to differentiate it from pancreatico-biliary subtype as it has worser prognosis. Detailed gross examination is important with more emphasis to the margins, perineural and lymphovascular invasion is important, so as to effectively and appropriately determine the stage and treatment of the patient.

Keywords: Whipple's pancreaticoduodenectomy, Pancreatic tumors, Intestinal adenocarcinoma, Pancreatico-biliary adenocarcinoma.

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1. Introduction

Whipple's pancreaticoduodenectomy (PD) is performed for operable tumors of ampullary, periampullary region, head of pancreas, common bile duct and duodenum, as well as for benign diseases that mimic malignancies.[1] In PD, a wide part of head of pancreas, duodenum from the pylorus to the ligament of Teitz, proximal jejunum, distal extrahepatic biliary tract, gallbladder along with cystic duct and occasionally distal part of stomach are removed based on the site of the tumor and type of the surgery.[2]

Whipple's PD encompasses ampullary carcinoma, periampullary carcinomas, duodenal carcinoma, pancreatic tumors and bile duct carcinomas. The most common histological type is adenocarcinoma followed by neuroendocrine tumour and mixed tumours.[3]

Clinically, these tumors remain silent until they cause obstruction or invade adjacent structures and often present with abdominal pain and weight loss accompanied by progressive jaundice and deep vein thrombosis in advanced cases. Among all the carcinomas pancreatic cancer is the third leading cause of cancer deaths, has highest mortality rate with a 5 year survival of 10%.[4]

Location, origin and histological type of tumor in Whipple's surgery is important as prognosis and staging criteria of the different tumor varies.[5] Neoadjuvant chemotherapy is recommended for pancreatic tumors only.

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Morphological evaluation of Whipple's pancreaticoduodenectomy (PD) enables to detect the gross origin of the primary tumor. Because of the intimate location of many structures in this area, benign lesion can cause obstructive symptoms, often mimics malignancy.[2]

Histopathology is the gold standard in Whipple's PD. In this background study was taken up to evaluate histomorphological profile of various lesions and to sort according to site, size, grade, nodal and marginal status.

2. Materials and Methods

The present study is a cross-sectional retrospective study conducted on all cases of Whipple's PD received in department of Pathology at ESICMC&PGIMSR, Bangalore. Total duration of study is 7 years.

2.1. Inclusion criteria

All Whipple's resection specimens received in the Department from January 2017 to January2024.

2.2. Exclusion criteria

1. Specimens with prior of neoadjuvant treatment.
2. Endoscopic biopsies were excluded from the study.

The study was undertaken after obtaining ethical clearance from Institutional Ethics committee. Clinical details were collected from the department case files and medical records. Radiological details and nature of surgery were noted.

Grossing techniques were adopted from Tata memorial dissection method.[5] Gross morphological features like nature of surgery, size and site of lesion noted on external appearance. The specimen is then cut along the greater curvature of stomach, anterior wall of pylorus and greater curvature of duodenum. The probe is placed in common bile duct (CBD) towards ampulla and along the main pancreatic duct. CBD is identified by greenish colour and tubular appearance. If cholecystectomy specimen received, then probe is inserted to identify the CBD. Ducts opened along the probe. On cut surface, the size, origin, consistency, appearance and extension of tumor noted. Cystic and necrotic changes if any were recorded.

Tumors were categorised as below[7-12] [**Figure 1-3**],

1. Tumors with epicentre in the ampulla as ampullary carcinomas.
2. Tumors growing circumferentially around the ampulla as periampullary carcinomas.
3. Tumors with both ampullary and periampullary growth patterns were categorized as mixed ampullary /periampullary carcinomas.
4. Tumors involving the circumference of the common bile duct as common bile duct tumors.
5. Tumors with epicentre in the duodenal wall exhibiting thickening or ulcero proliferative growth protruding into the lumen as duodenal carcinomas.
6. Tumors distinctly noted in head and body of pancreas as pancreatic carcinomas.

Representative bits processed, 3- 4 micron sections cut and H&E stained slides were studied microscopically and reported according to CAP protocol, AJCC 8th edition [9].Histopathological type, grading, origin of the tumour, lymphovascular, perineural invasion, margin status and lymph nodes involved were studied. Pancreatic neck margin, cystic duct margin, uncinate margin, superior mesenteric vein/portal vein and gastric/duodenal margins were assessed microscopically. Sections from anterior and posterior surface of the pancreas are also evaluated for tumor involvement. TNM staging of the tumour is done based on AJCC TNM classification. Histological grading was based on the extent of glandular differentiation of tumor as

G1: Well-differentiated (>95% glands)
G2: Moderately differentiated (50-95% glands)
G3: Poorly differentiated (5-49% glands)
G4: Undifferentiated (<5% glands)

Immunohistochemistry was done on formalin fixed paraffin embedded blocks using peroxidase antiperoxidase method with secondary antibody from Biogenix manufacturer. Markers like CK7, CK20, CDX2, MUC1, Chromogranin and synaptophysin were applied wherever necessary based on histological type.

3. Results

During the study period, 20 cases of Whipple's PD were received in department of Pathology constituting0.06%of total specimens. Of the 20 cases, 8 cases underwent Pylorus preserving PD and 11 cases with Classical Whipple's surgery. One case was extended Whipple's surgery with removal of spleen. Of the study group, age range was 40-73 years with the mean age of 55.2years. Majority were males with male to female ratio of 1.5:1.Obstructive jaundice is the commonest clinical presentation in 14cases (70%) and history of abdominal pain was obtained from 6 patients (30%).

Malignancy was seen in 19 cases (95%) and remaining one case (5%) was benign inflammatory condition. The mean size of the tumor was 2.7 cm and the range being 1-7cms. The most common location is the periampullary region seen in 6 cases (31.5. %). The next commonest location was duodenum seen in 5 cases (26.3%). Ampullary and mixed periampullary-ampullary location was seen 2 cases each (10.5%). Tumors arising from the head of the pancreas were seen in 4 cases (21.1%) [**Figure 1**].

Table 1: Sociodemographic distribution with type of surgery, site and size of tumor

S.No.	Age in years	Sex	Clinical features	Type of surgery	Site	Size in cm
1	42	Male	Jaundice	CW	Periampullary (D2)	7x5.5
2	40	Male	Jaundice	CW, GB	Periampullary & Head of pancreas	4x1.8
3	60	Female	Jaundice	PPPD	Periampullary	3x1.5
4	62	Male	Jaundice Cholelithiasis	PPPD	Periampullary	1x0.8
5	65	Male	Jaundice	PPPD	Periampullary	1x0.5
6	51	Male	Jaundice	CW and proximal jejunum	Periampullary	3.6x3.2
7	58	Female	Jaundice, Pain	PPPD	Mixed	4x2
8	55	Male	Jaundice	CW	Mixed	1x1
9	53	Female	Jaundice	CW and Jejunum	Ampullary	2.5x1.2
10	40	Female	Jaundice	PPPD	Ampullary ca	1x1
11	64	Male	Pain	CW	Pancreas-uncinate, 1cm from CBD	3.5x2.2
12	54	Male	Jaundice	CW and Jejunum	Head of pancreas	2.5x2.5
13	57	Male	Pain	PPPD	Head of pancreas	2x2
14	40	Female	Pain	PPPD and splenectomy	Pancreas	4.1x3.9
15	56	Female	Jaundice, Pain	CW	Duodenum	1.6x1
16	70	Female	Jaundice	PPPD	Duodenum	1.4x1.1
17	67	Male	Jaundice	CW	Duodenum	4.5x3
18	54	Male	Pain	PPPD	Duodenum	1.5x1
19	73	Female	Jaundice	CW	Duodenum	3x0.8
20	42	Male	Jaundice	CW and Proximal jejunum	-	5x3

Table 2: Grade, subtype, TNM staging, lymphovascular invasion/ perineural invasion, with status of lymph node metastasis and margins of the tumor

S.No	Grade and subtype	TNM	LVI	PNI	LN status	Margins
1.	G1, PB	T3N2MX	Absent	Absent	6/10	Uncinate process: Involved
2.	G2, PB	T4N1MX	Present	Absent	1/1	Uninvolved
3.	G1, Intestinal	T2NOMX	Absent	Absent	0/0	Uninvolved
4.	G1, Intestinal	T2N0MX	Absent	Absent	0/8	Uninvolved
5.	G1, Intestinal	T2NXMx	Absent	Absent	0/1	Uninvolved
6.	G2& NET G3 Duodenum Intestinal	T3aN1MX	Absent	Absent	1/14	Close but Uninvolved
7.	G2, Intestinal	T2NOMX	Absent	Absent	0/0	Uninvolved
8.	G1, Intestinal	T2N1MX	Absent	Absent	2/7	Uninvolved
9.	G2, Intestinal	T4N0MX	Absent	Absent	0/18	Uninvolved
10.	G2, Intestinal	T1N1MX	Absent	Absent	2/8	Uninvolved
11.	G2, PB	T2N1Mx	Present	Present	0/3	Uninvolved
12.	G2, PB	T2NOMX	Absent	Absent	0/0	Pancreatic margin involved
13.	G2, PB	T1cN1MX	Present	Present	1/6	Retroperitoneal margin involved
14.	G2, NET	T2N0MX	Present	Absent	0/7	Posterior margin involved
15.	G2, Intestinal	T3NoMx	Absent	Absent	0/9	Uninvolved
16.	NET G2	T3N0MX	Absent	Absent	0/0	Uninvolved
17.	G2, Intestinal	T4N2Mx	Absent	Absent	4/7	Uninvolved
18.	G1, NET	T1N0MX	Absent	Absent	0/0	Uninvolved
19.	G1, Intestinal	T2N1MX	Absent	Absent	1/3	Uninvolved
20.	Chronic pancreatitis	-	Absent	Absent	0/8	-

(LVI: Lymphovascular invasion, PNI: perineural invasion, LN: lymphnode)

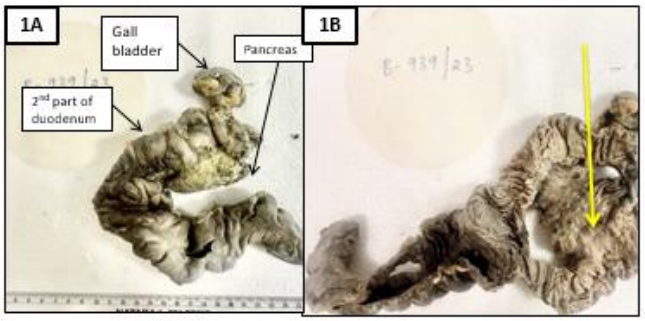

Figure 1: Whipple's pancreatico-duodenenctomy specimen; **A:** External surface and **B:** Cut surface showing growth in periampullary region

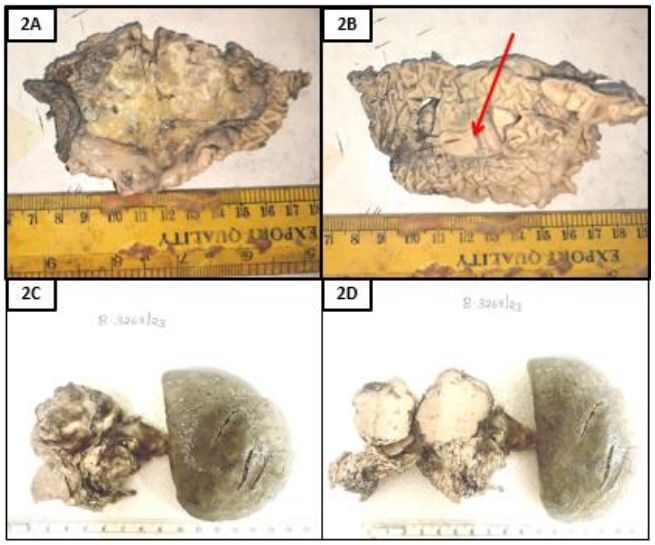

Figure 2: A & B: Whipple's pancreaticoduodenectomy specimen-external surface and cut surface respectively, showing 1.4x1.1 cm nodule in the duodenum (Red arrow). Diagnosed as Neuroendocrine tumor (G2); **C** & **D:** Whipple's pancreaticoduodenectomy with splenectomy showing 4.1x3.9 cm well circumscribed tan brown tumor in pancreas (Black arrow) with adjacent normal pancreas (Red arrow). Diagnosed as Neuroendocrine tumor stage IB.

Histologically Intestinal type adenocarcinoma was seen in 11 cases (68.8%), and pancreaticobiliary (PB) type in 5 cases (31.2%). Intestinal type adenocarcinoma was the microscopy in 3 cases (27.3%) of duodenum, 4 cases (36.3%) of periampullary region and 2 cases (18.1%) each in ampullary and mixed ampullary periampullary region. Microscopically exhibit neoplastic glands lined by tall columnar cells with elongated pseudo stratified nuclei and few scattered goblet cells [**Figure 6A,B,C**].

PB type adenocarcinoma was seen in 3 cases (60%) of pancreas and 2 cases (40%) of periampullary carcinomas, microscopically exhibiting small neoplastic glands in a desmoplastic stroma. The glands are lined by single layer of cuboidal to columnar cells with round nuclei devoid of stratification [**Figure 6**D]. On IHC, CK7 was performed in 3 cases of PB type and found to be positive (100%). CDX2 was negative in all cases of PB adenocarcinoma.

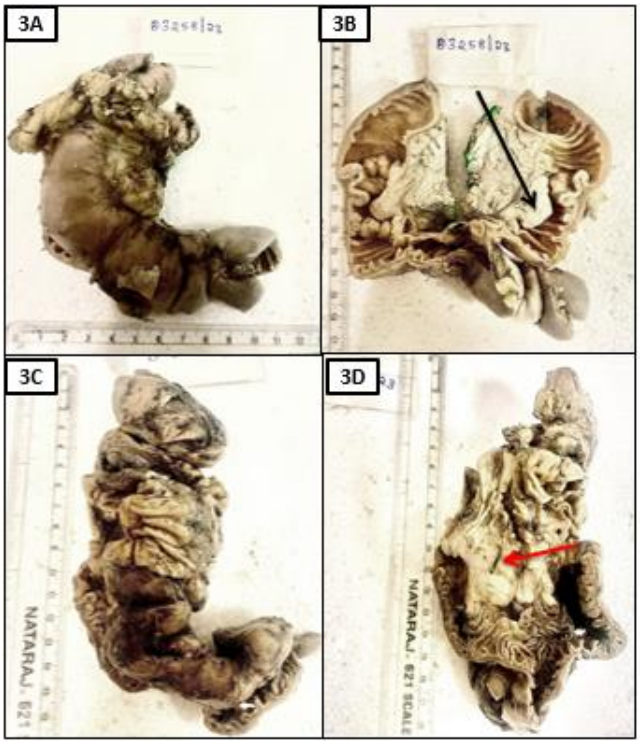

Figure 3: A & **B:** Whipple's pancreaticoduodenectomy specimen showing 2.5x1.2 cm mass in ampullary region (Black arrow). Diagnosed as Adenocarcinoma of the duodenum stage IIB; **C** & **D:** Whipple's pancreaticoduodenectomy specimen showing mass in the 2nd part of duodenum partially obstructing the lumen. Diagnosed as Adenocarcinoma of duodenum stage IIB.

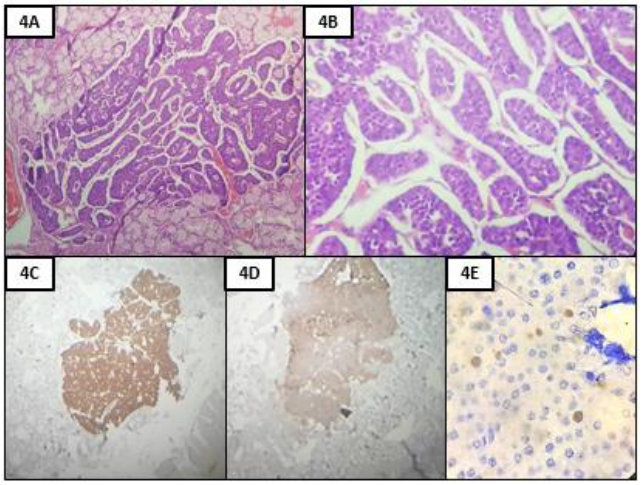

Figure 4: A & **B:** Microscopy of tumor nodule in the Duodenum showing nests of tumor cells having oval nuclei with salt and pepper chromatin, diagnosed as Neuroendocrine tumor, Grade 3; **C** & **D:** IHC showing Synaptophysin and chromogranin Positivity; E :Ki67: 35%.

Neuroendocrine carcinoma (NEC) was seen in 4 cases (21.1 %) of which 3 cases seen in duodenum (G1,G2 &G3 each) and 1 case in pancreas (G2), microscopically display nests of tumor cells separated by fibro vascular septae. Tumor cells were uniform with round to oval nuclei having salt and pepper chromatin. Ki67 showed mitosis of <3% in Grade 1

and 3-20% in Grade 2 tumors. On IHC, Chromogranin and synaptophysin was positive in all cases with negative CK7 and CK20 [**Figure 4**,**5**].

Mixed NEC with intestinal type adenocarcinoma was seen in one case, showed features of neuroendocrine carcinoma grade 3in duodenum distinctly away from the periampullary growth.

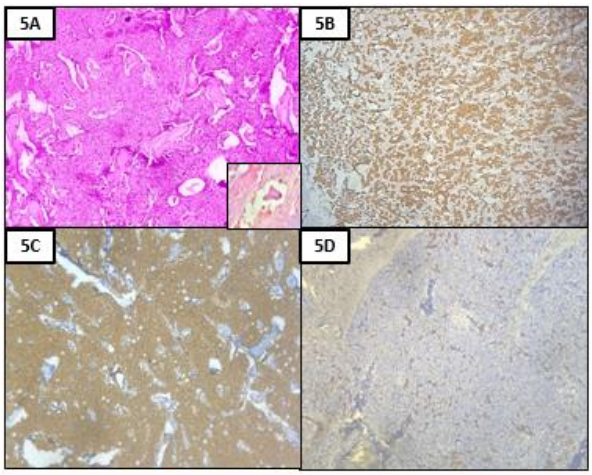

Figure 5: A: Microscopy of neuroendocrine tumor in the pancreatic head with tumor cells in solid nests. Individual tumor cells are small having uniform round nucleus with stippled chromatin. Inset showing: Lymphovascular invasion of tumor cells; **B** & **C:** IHC positive for Chromogranin and synaptophysin; **D:** IHC showing CK7 Negative.

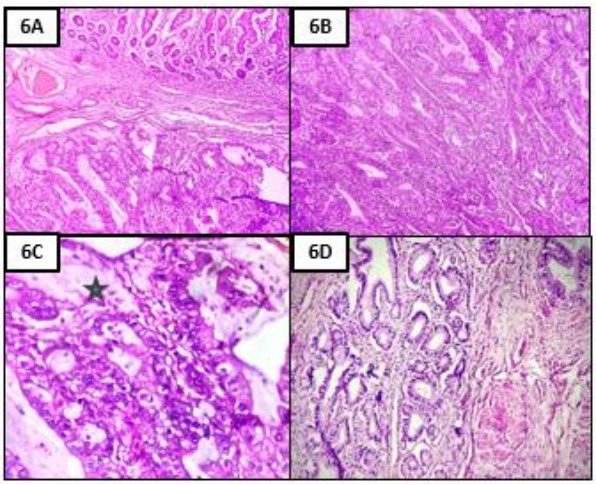

Figure 6: Microscopy of Periampullary Adenocarcinoma; **A, B** & **C** (H&E 4X,10X and 40X respectively): Intestinal type, arising from the duodenal surface of the ampulla invading into the submucosa . Individual tumor cells showing loss of nuclear polarity, pseudostratification, enlarged vesicular nucelus and prominent nucleoli. Also noted pools of mucin in the stroma<50%.; **D:** Biliary type Periampullary adenocarcinoma showing glandular arrangement of tumor cells invading into the muscularis layer, separated by desmoplastic stroma. The glands are lined by single layer of cells have columnar cells with scant luminal mucin.

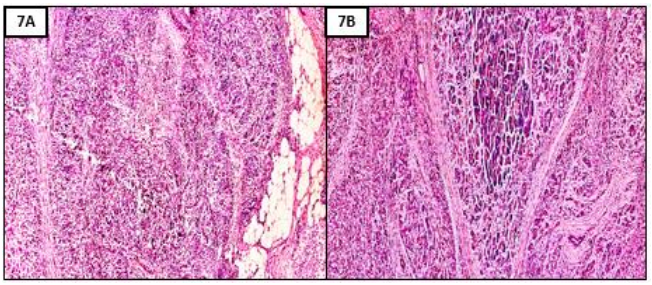

Figure 7: A & **B:** Microscopy of chronic pancreatitis showing atrophied glands surrounded by fibrosis and lymphoplasmacytic infiltrates.

In present study, we had single case of chronic pancreatitis in 42-year-old male, clinically presented with symptoms of obstructive jaundice. Microscopically characterised by fibrosis with diffuse chronic inflammatory infiltrate and lack of acinar tissue [**Figure 7**].

Lympho-vascular invasion (LVI) was seen in 3 cases (75%) of pancreatic tumors and 1 case (10%) in periampullary adenocarcinoma. Two cases (or 50%) of pancreatic tumours had perineural invasion (PNI); however, it was absent in ampullary and periampullary carcinomas. Margins were positive in 75% of pancreatic tumors and 10% of periampullary carcinoma. Lymph node metastasis was seen 8 cases (42.1%). Histological grading showed 9 cases (56.2%) with moderately differentiated type-G2 and 7 cases (43.8%) of well differentiated adenocarcinoma-G1. On TNM staging, 50% (8/16 cases) belonged to T2. Three cases (18.8%) each under T3 & T4 and 2 cases (12.5%) of T1 [**Table 2**].

4. Discussion

Whipple's PD was first demonstrated by Allen. O Whipple in 1935.[13] Whipple AO performed a total of 37 pancreatico-duodenectomies of which 30 were for periampullary carcinomas and seven for chronic pancreatitis.[4] He proposed various modifications to the original one stage procedure which significantly improved the mortality associated with this surgery.[13,14] Whipple's PD is the most complex surgeries performed for the management of tumours involving the head of pancreas, duodenum, ampulla of Vater and common bile duct.[7] A thorough knowledge of the gross anatomy, proper orientation of the specimen and identification of important margins like pancreatic neck margin, uncinate margin and the common bile duct margin is important. Pancreatic, ampullary and distal bile duct cancers have different prognosis and staging. In large tumours of this region accurate identification of the origin of the tumour may be difficult even for most experienced pathologists because of the proximity of the anatomical structures. Hence careful sectioning of the pancreatic head is important as Feakins R. et al., study surveyed that 87% histopathologists distinguished between intrapancreatic bile duct carcinoma from pancreatic carcinoma.[15] Hence axial method of dissecting the head of pancreas is followed among many other methods.[12,16,17]

A Whipple's PD specimen can be one of the following types

1. Classic Kausch-Whipple's procedure which contains distal stomach and pylorus.
2. A pylorus preserving pancreatoduodenectomy (PPPD) wherein the duodenum is transected 1-2 cm distal to the pylorus.
3. Extended Whipple's involves retroperitoneal and aortocaval lymph node dissection.

The mean age of presentation in our study is 55.2 years with male preponderance in concordance with study done by Amin et al, Dahkwa et al, and Sararee et al.[4,18,19] Clinically jaundice was the most symptom in the present study similar to studies conducted by Jakhmola et al and Sararee et al.[19,20]

Periampullary carcinoma was the most common tumor followed by duodenal and pancreatic carcinoma. Amin et al and Dhakwa et al also reported periampullary carcinoma to be the most common tumor.[4,18] Microscopically majority are adenocarcinomas and histological subtyping into Intestinal, PB or mixed is important. Westgard et al., opined PB type adenocarcinoma is independently associated with poor prognosis.[21] In our study intestinal type was most common histological subtype of adenocarcinoma seen in 68.8% cases (11/16) while PB type adenocarcinoma was the microscopic feature in 5/16 cases (31.2%) similar to study conducted by Howe et al.[22] PB adenocarcinoma showed PNI in 40% cases and LVI in 60% cases. Also, lymph node metastasis was seen in 80% of cases which was much higher compared to intestinal type adenocarcinoma.

On histological grading, 9 cases belonged to moderately differentiated type (56.25%) and remaining 7 cases showed well differentiated adenocarcinoma, similar to Sararee et al Y & Howe et al.[19,21] Dhakwa et al., also found well and moderately differentiated to be the most common grade.[18]

Lymphnode positivity in ampullary and periampullary carcinoma is an independent adverse prognostic factor.[23,24] Lymph node retrieval during grossing can be improved by 2 methods, one is radially sectioning uncinate margin and submitting entirely for processing.[25,26] The other method advocated by Adsay et al., is orange peel method which increased the mean lymph node from 6.1 to 14 in their study.[27] In the present study lymph node involvement was seen in 42.1% of cases which is similar to studies conducted by Warren KW et al.,Allema JH et al., and Sararee et al., who showed metastasis in 29-52%, 40% and 35.1% respectively.[19,28,29]

PNI and LVI are again an independent prognostic factor for long term survival.[30,31] In our study pancreatic tumors showed PNI and LVI in 50% (2/4) and 75% (3/4) respectively, while in ampullary and periampullarycarcinoma, LVI was seen in 10% cases and PNI was absent in all cases.

With respect to margin status positivity, European's follow 1 mm[18]**Error! Reference source not found.**-[33] while zero mm clearance with presence of tumor at the inked margin was considered positive by American pathologist. We followed zero mm clearance and found that 80% (16/20 cases) achieved margin clearance. This was similar to studies conducted by Amin pd et al, (83.7%).Yeo CJ et al in their study achieved margin clearance of 71% and 97% in pancreatic and ampullary carcinoma respectively.[33]

On TNM staging of adenocarcinomas, majority of cases belonged to T2 (8/16 cases), followed by T3 & T4, similar to Manan shah et al study.[34]

The prevalence of benign disease in Whipple's procedure for suspected malignancy ranges from 8.4% to 15.6%. The benign mimicker of the carcinoma includes adenomyoma of ampulla, Papillary hyperplasia, sclerosing papillitis and anatomic pancreatitis.[35] In our study 1 case (5%) belonged to chronic pancreatitis with symptoms of obstructive jaundice and was mimicking clinically as ampullary carcinoma.

5. Conclusion

Meticulous grossing and proper orientation of the specimen, identification of margins is important as pancreatic, ampullary, duodenal and distal bile duct carcinomas have different prognosis and staging. Histological subtyping of adenocarcinoma into pancreticobiliary or intestinal type is necessary as PB type has worse prognosis.

6. Source of Funding

None.

7. Conflict of Interest

None.

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