

A RETROSPECTIVE HISTOPATHOLOGICAL STUDY OF WHIPPLE'S RESECTION SPECIMENS AT TERTIARY CARE HOSPITAL

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Abstract

Background: Pancreaticoduodenectomy otherwise called Whipple's procedure was first demonstrated by Allen O. Whipple in 1935. It involves surgical resection of pancreatic head. Duodenum, distal stomach, distal common bile duct and gall bladder.

Materials and methods: This is the retrospective study of cases done during March 2019 to June 2023. All the cases on which Whipple's surgery was done were received from the records. The details about the gross examination of the specimen were taken from the records.

Results: 45 Whipple's specimen were received during our study period. Out of them, 30 cases were male and 15 cases were female. The male:female sex ratio is 2:1 in our study. When the age incidence of pancreatic carcinoma was calculated the mean age of occurrence in our study was 51.5 years. The youngest case of carcinoma in our study was 29 years old male. The oldest case in our study was 70 years old male. Average age of presentation in male was 51 years and average age of presentation in females was 55 years. Neither familial clustering nor familial syndromes were seen in our studies.

Conclusion: Pancreaticoduodenectomy specimen requires meticulous histopathological evaluation for proper categorisation of histopathological types and other features which affect patient survival following PD. Possibility of a benign diagnosis remains in PD specimens which have been resected presuming malignancy based on clinical judgement and radiological data.

The result found in our study were:

- Total 45 Whipple's specimens received in our study.
- Out of it. 41 were malignant, 3 were benign and 1 was non-neoplastic.
- Youngest case was 21 years old and oldest case was 70 years. Mean age was 51.42 years with 2: 1 male predominance.
- Periapillary region is most common site for tumor location(62.3%).
- 57.8% cases show tumor size (2 cm).
- Benign lesions in our study were: Microcystic serous cystadenoma, Acinar cell cystadenoma and PanIN grade 2.
- We used Axial slicing method and Bi-valving method for grossing.
- We found that Axial slicing method is more beneficial than Bi-valving in cases of pancreatic Ductal Adenocarcinoma.
- Bi-valving method more beneficial than axial slicing method in cases of cystic pancreatic tumors.
- In Bi-valving method, periampullary region is always visualized and primary origin of periampullary tumors (pancreas, duodenum, CBD, ampulla of Vater) can be more appreciated.
- One case of PanNET was functional and show histology of Somatostatinoma. It was the known case of Neurofibromatosis I and patient had multiple well defined skin nodules. In the specimen multiple nodule were found in small intestine and it show histology of Gastro intestinal stromal tumor

- One non-malignant case was Cystic dysuophy of Heterotropic duodenal wall (groove pancreatitis) which is rare.
- 35(85.3%) cases were PDAC and Moderately differentiated Adenocarcinoma(58.7%) was most common histological type.
- The incidence of lymphnode involvement is higher in cases of PDAC. In our study,13 cases (37.1%) cases show lymphnode involvement. Incidence of perineural invasion is also higher 48.5% associated with poor prognosis.
- 3 cases show margin involvement. In 2 cars retroperitoneal margin was involved and in 1 case superior mesenteric vessel margin was involved.

Key words: Whipple’s resection specimen, Pancreatic Ductal adenocarcinoma, PanNet, Pancreas.

INTRODUCTION

Pancreaticoduodenectomy otherwise called Whipple's procedure was first demonstrated by Allen O. Whipple in 1935. It involves surgical resection of pancreatic head. Duodenum, distal stomach, distal common bile duct and gall bladder. This surgery is done for perinmpullury carcinoma, ampullary carcinoma, pancreatic tumors, and tumors of the pancreatic duct, turmors of common bile duct, duodenal carcinoma and sometimes for chronic pancreatitis. Over 80% of the tumors in this region are adenocarcinoma. Tumors in this region are mostly seen among elderly age group and surgery is the only means of curing them. Because of intimate location of many structurcs in this area even a benign condition may cause obstructive symptoms.

Whipple's surgery has been done on those benign conditions as they mimic malignancy and histopathology is the gold standard when such situation arises.

In this study we present the results of 8-year review of pathological findings in Whipple's surgical specimen in Dhiraj hospital. Pathological assessment of surgical specimens from Whipple's surgery needs spccial attention in order to accurately evaluate many factors that are prognostically important. These factors include tumor location, extension, size, histological type and grade, Surgical margin status, vascular or perineural invasion and lymph node status. Along with that the age and sex incidence are also analysed.Comparison of the incidence of our hospital with other literatures is also attempted.

MATERIALS AND METHODS

This is the retrospective study of cases done during March 2012 to December 2019. All the cases on which Whipple's surgery was done were received from the records. The details about the gross examination of the specimen were taken from the records.

RESULTS

TABLE 1: DISTRIBUTION OF TUMORS ACCORDING TO THEIR GENDER.

TOTAL CASES	45	%
Males	30	66.7
Females	15	33.3

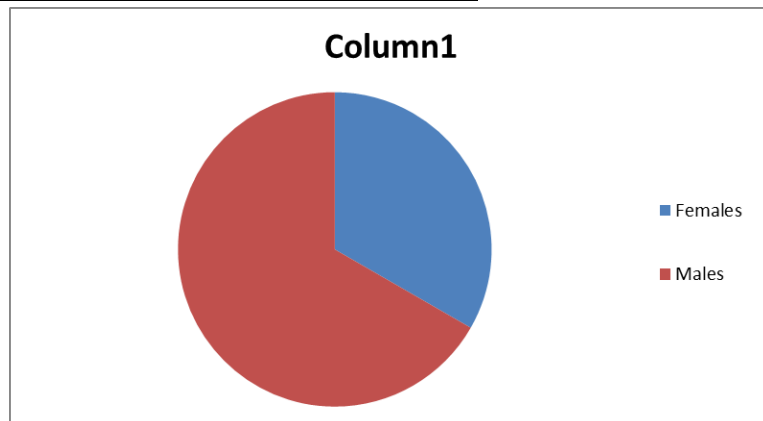


TABLE 2: DISTRIBUTION OF LESIONS

Benign	02	4.4%
Non Neoplastic	01	2.2%
Malignant	42	93.4%
Total	45	100%

TABLE 3: DISTRIBUTION OF TUMOURS ACCORDING TO THEIR LOCATION

Location	Male	Female	Total	Percentage
Ampullary	4	2	6	13.3
Periampullary	20	8	28	62.3
Head of Pancreas	3	3	6	13.3
2 nd part of duodenum	3	2	5	11.1
Total	30	15	45	100

TABLE 4: DISTRIBUTION OF TUMOURS ACCORDING TO THEIR SIZE IN CENTIMETRES:

Location	Up to 2 cm	2.1 to 3 cm	3.1 to 4 cm	>4 cm
Ampullary	6	0	0	0
Periampullary	17	7	1	3
Head of pancreas	1	4	0	1
2 nd part of duodenum	2	0	1	2
Total	26	11	2	6

TABLE 5: DISTRIBUTION OF PDAC ACCORDING TO HISTOLOGICAL TYPES AND GENDER

Histological type	Male	Female	Total
Well differentiated adenocarcinoma	3	1	4
Moderately differentiated adenocarcinoma	17	7	24
Poorly differentiated adenocarcinoma	5	2	7
Total	25	10	35

TABLE 6: DISTRIBUTION OF HISTOLOGICAL TUMOUR TYPES ACCORDING TO LYMPHO VASCULAR INVASION, PERINEURAL INVASION AND LYMPHNODE STATUS

Histological types	Lymphovascular Invasion		Perineural invasion		Lymphnode status	
	Present	Absent	Present	Absent	Uninvolved	Involved
Well differentiated adenocarcinoma	0	4	2	2	3	1
Moderately differentiated adenocarcinoma	9	15	12	12	15	9
Poorly differentiated adenocarcinoma	4	3	3	4	4	3
Non invasive intraductal papillary neoplasm	0	1	0	1	1	0
Neuroendocrine tumor	0	4	1	3	0	4
Acinar cell carcinoma	1	0	1	0	1	0
Pancreatic intraepithelial neoplasm	0	1	0	1	1	0
Total	14	28	19	23	25	17
%	34.1	65.9	46.3	53.7	58.5	41.5

TABLE 7: DISTRIBUTION OF HISTOLOGICAL TUMOR TYPES ACCORDING TO LYMPHOVASCULAR INVASION, PERINEURAL INVASION AND LYMPHNODE STATUS IN PDAC CASES

Histological types	Lymphovascular Invasion		Perineural invasion		Lymphnode status	
	Present	Absent	Present	Absent	Uninvolved	Involved
Well differentiated adenocarcinoma	0	4	2	2	3	1
Moderately differentiated adenocarcinoma	9	15	12	12	15	9
Poorly differentiated adenocarcinoma	4	3	3	4	4	3
Total	13	22	17	18	22	13
%	37.1	62.9	48.5	51.5	62.9	37.1

TABLE 8: DISTRIBUTION OF HISTOLOGICAL TUMOUR TYPES ACCORDING TO SURGICAL MARGIN STATUS

Histological type	Surgical margin status	
	Involved	Uninvolved
Well differentiated adenocarcinoma	0	4
Moderately differentiated adenoma carcinoma	2	22
Poorly differentiated adenocarcinoma	0	7
Non invasive intraductal papillary neoplasm	0	1
Neuro endocrine tumour	1	3
Acinar cell carcinoma	0	1
Pancreatic intraepithelial neoplasm	0	1
Total	3	39
%	7.1	92.9

TABLE 9: DISTRIBUTION OF PANCREATIC DUCTAL ADENO CARCINOMA CASES ACCORDING TO STAGE

STAGE	T1	T2	T3	T4
NUMBER OF CASES	2	12	17	4

TABLE 10: COMPARISON OF GENDER INCIDENCE IN DIFFERENT STUDIES.

Gender Incidence	Total No. cases	Males(%)	Female(%)
Present study	45	66.7	33.33
Kumar NV	29	55.2	44.8
Hasan MM et al	808	55.6	44.4
Anderson LN et al	422	55	45
Dickinson KJ et al	31	51.61	48.4

TABLE 11: CONIPARISON OF MEAN AGE AND AVERAGE % OF CASFS IN DIFFERENT AGE GROUPS IN DIFFERENT STUDIES.

Age in years	Kumar NV	Hasan MM et al	AnnuSumi Issac	Present study
<40	10.3%	1.9%	-	24.4%
41-50	34.5%	11.9%	41.7%	24.4%
51-60	20.7%	29.2%	8.3%	28.9%
61-70	24.1%	35.7%	41.7%	22.3%
>70	10.3%	21.3%	8.3%	-
Mean age	51.17	61.9%	59.1	51.4

Table 12

Studies	Adenocarcinoma intestinal type	Adenocarcinoma pancreaticobiliary type	Acinar type	Duodenal carcinoma	Bile Duct Carcinoma	panIN	Solid pseudo papillary tumour	Pancreatic endocrine tumor	Benign lesions
Shifa et al	63%	6.7%	-	-	-	-	3.3	6.7%	20%
Howe et al	76%	27%	-	-	-	-	-	-	-
Yeo et al	81%	-	-	7%	12%	-	-	-	-
Chan C et al	91%	-	-	3%	5%	-	-		
Michelas si F et al	89.3%	-	-	2.5%	6.2%	-	-		
Our study	68.9%	2.2%	2.2%	6.7%	-	2.2	-	8.9%	4.4%

45 Whipple's specimen were received during our study period. Out of them, 30 cases were male and 15 cases were female (Table 1). The male:female sex ratio is 2:1 in our study. When the age incidence of pancreatic carcinoma was calculated the mean age of occurrence in our study was 51.5 years. The youngest case of carcinoma in our study was 29 years old male. The oldest case in our study was 70 years old male. Average age of presentation in male was 51 years and average age of presentation in females was 55 years. Neither familial clustering nor familial syndromes were seen in our studies. Out of 45 total patient 30 (66.7%) was male and 15 (33.3%) was female (Table 1). Out of 45 total cases of PD, 42 (93.47%) were found to be malignant, 2 (4.4%) were found to be benign and 1 (2.2%) case was found non-neoplastic lesion (Table 2). The benign conditions that we encountered were Microcystic serous cystadenoma and Acinar cell cystadenoma. The non-neoplastic condition was cystic dystrophy of heterotropic pancreas of duodenal wall. The malignant conditions encountered were PDAC. Acinar cell carcinoma and PanNET. Maximum tumour dimension, tumour differentiation, number of lymphnode dissected, lymph node status, lymphovascular and perineural invasion among the different adenocarcinomas are studied. Out of 45 specimens, most of the tumours were located in periampullary region. 28 tumours were located in periampullary region. It constitutes around 62.3% of the cases in our study. Next most common site were head of pancreas (13.3%) and ampullary region (13.3%) followed by 2nd part of duodenum (11.1%) (Table 3). In our study, total 26 tumours were measuring up to 2 cm. It constitutes around 57.8% of the total tumours in our study. Out of these 26 tumours 17 were located in periampullary region. It constitutes around 65% of total tumours measuring up to 2 cm (Table 4). Out of 42 malignant cases, 35 cases (83.3%) were of pancreatic ductal adenocarcinoma. Among these 35 cases of PDAC, 3 were arising from duodenum. Most common histological type in our study is Moderately Differentiated adenocarcinoma. Out of 42 malignant tumours, 24 were moderately differentiated adenocarcinoma histological subtypes. It constitutes around 57.1% of tumours in our study. Followed by Poorly differentiated adenocarcinoma (16.7%). Well differentiated adenocarcinoma (9.5%). Pancreatic neuroendocrine carcinoma (9.5%). Non-invasive pancreatic intraductal Neoplasm (2.4%), Pancreatic intraepithelial neoplasia grade II (2.4%) and acinar cell carcinoma (2.4%). Usually PanNETs are non-functional but in our study, 1 case was functional and histologically correlates with Somatostatinoma. It was known case of neurofibromatosis I and there were multiple small nodules found in small intestine which show the histology of GIST. In our study highest numbers of cases were noted in age group of 51-60 years. Out of 35 cases of PDAC, most of the patients belonged to age group of 41-50 years and 51-60 years constituting 10 cases (28.47%) each (Table 5). Lymphovascular and perineural invasion varied in different tumor subtypes. In our study, 14 cases showed presence of lymphovascular invasion. It constitutes around 33.3% of total cases. In our study, 19 cases showed presence of Perineural invasion. It constitutes of around 45.2% of total cases. The lymphnode involvement by tumour varied in different tumor types. In our study, 17 cases showed evidence of lymphnode Metastasis. It constitutes around 40.5% of total cases. Lymphnodes were involved in all 4 cases of Pancreatic neuroendocrine tumour (100%) (Table 6). The incidence of lymphnode involvement is higher in cases of PDAC. In our study, 13 cases (37.1%) cases show lymphnode involvement. Incidence of perineural invasion is also higher 48.5% associated with poor prognosis (Table 7). In our study, 3 cases showed presence of positive surgical margin status. It constitutes around 7.1% of total malignant cases. 2 cases from Moderately

Differentiated Carcinoma and 1 case from neuroendocrine tumour show surgical margin status positive. In Moderately Differentiated Adenocarcinoma, one case show SMV and Retroperitoneal margin involved while other case shows only SMV margin involved. In Neuroendocrine tumour only retroperitoneal margin was involved (Table 8). Tumor size (defined as the largest dimension of the tumor as assessed at pathology) is a well established predictor of survival in PDAC and determines T category for tumors limited to the pancreas. According to AJCC TNM 8n edition pancreatic soft tissue involvement is no longer a factor in determination of T category. T1-T3 is depended only on tumor size, while T4 requires tumor involvement of the celiac axis, superior mesenteric artery and/or common hepatic artery. Out of 35 cases of pancreatic ductal adenocarcinoma, 5 show evidence of chronic pancreatitis which constitutes 14% in our study. Pancreatic fistula is the most common and serious complication of PD surgery. The safety of the pancreatic anastomosis is closely related to the quality of the pancreatic remnant. In Whipple's procedure if the remnant pancreas after surgery shows histology of chronic pancreatitis (hard pancreas). The chances of anastomotic leak are around 8%. It can reach up to 14% to 23% when the pancreatic parenchyma is normal (soft pancreas). Most of the other serious complications in these patients are as result of pancreatic leak (Table 9).

DISCUSSION

This study was done at Dhiraj hospital pathology department, SBKS MI & RC, Waghodia, Vadodara. The Whipple's procedure is one of the most complex surgeries performed for the management of a variety of tumours involving the head of pancreas, Ampulla of Vater, common bile duct, or second part of duodenum. Ampullary region as such unique as it contains both duodenal and the ductal epithelium. The normal ampullary mucosa is identified as paler columnar cells admixed with many goblet cells that indent the duodenal mucosa. It is composed of more complex and branched submucosal glands. Distinguishing the intramucosal or in situ involvement from the invasive Ampullary carcinoma is difficult for the young pathologists. Lobular glandular architecture with lamina propria surrounding the glands and absent stromal response are the clues to rule out the invasive component when such dilemmas arise ^[1] It has been reported that in many complicated cases of chronic pancreatitis, presenting as periampullary mass, the Whipple's procedure is now considered reasonable ^[2]. Our study shows valuable findings. In our study Periampullary region carcinoma was more prevalent among the Whipple's specimen (62.3 %) which in contrast to other studies. Duffy et al, Telamani et al and Howe et al reported ampullary carcinoma as the predominant cancer ^[3-5]. We found only 6 cases of ampullary region carcinoma. Pancreatic tumours are predominantly seen in males in their seventh decade. Although male gender has been proved to be an increased demographic risk, the present study also obtained male dominance which was higher when compared to other studies. Henson et al in their study had mentioned that mean age of incidence was 69.7 years, Howe et al mean age was 65.6 years ^[2], in Yeo JC et al's study mean age was 64 years ^[6]. In our study mean age of incidence was 51.42 year with male predominance. Youngest case in our study was 21 years male (Table 10). In Howe et al study, mean size of the ampullary tumour was 2.7 cm, in our study 61 % tumours were <2 cm. Western literature reveals pancreatic adenocarcinoma to be commonest finding in Whipple's specimen. In a review of 650 pancreaticoduodenectomies Yeo et al found 43% cases to be pancreatic adenocarcinoma ^[7]. We found 35 cases (77.8%) were of pancreatic ductal adenocarcinoma in our study. Histopathologically, the pancreatic adenocarcinoma can be intestinal type, pancreatobiliary type, mixed type and undifferentiated type. Categorization is important because the prognosis of intestinal type is better than pancreatobiliary type. We found only 1 case of pancreatobiliary type adenocarcinoma in our study. In Howe et al's study well and moderately differentiated graded tumours predominated. In our study, 53.3% tumours were moderately differentiated adenocarcinoma which is correlate with other studies. The nodal involvement was 37.1% in cases of PDAC in our study. In Warren K Wet al's study nodal metastasis ranged from 29-52% and in Allema JH et al's study it was 40% ^[8,11]. Which correlate with our study. The pancreatic neuroendocrine tumour (PanNET) is 5.25/1,00,000 represent 1% to 2% of all pancreatic neoplasm. The incidence of pancreatic endocrine neoplasm is less than 3% of all pancreatic neoplasms according to Henson et al. ^[9] its in our study 4 out of 45 cases were pancreatic neuroendocrine tumour which constitutes around 8.9% of all cases. One case was known case of Neurofibromatosis I and there were multiple small nodules found in small intestine which show the histology of GIST (Table 11) Yeo et al performed multivariate analysis of 443 cases and reported 4 factors found to adversely effect the survival: 1) tumour diameter >3 cm; 2) the presence of positive resection surgical margins; 3) the finding of lymphnode metastases in the resected specimen; and 4) the presence of poorly differentiated tumour. In our study, found majority of the tumour diameter is < 2 cm (57.8%). Moreover, in our study, 24 (53.3%) cases were moderately differentiated and 2 cases of it show resected surgical margin involvement. One case of well differentiated pancreatic NET show resected surgical margin involved. When lymphnode involvement by malignant tumour is taken into consideration including 4 NETS, 17 cases (41.5%)

showed lymphnode metastasis which is significantly higher as compare to study done by Ibrahim et al (10%) and similar to study done by Allema JH et al (40%)^[10,11] In the large series of 1175 resected pancreatic cancers by Winter et al, the incidence of perineural invasion was 91% whereas vascular involvement was lower 53%^[11]. In our study, patients with pancreatic cancer had 34.1% incidence of lymphovascular invasion and 46.3% incidence of perineural invasion which have been shown to be bad prognostic features.

Margin status has been shown to relate to survival outcomes. The SMV margin is most frequently involved by the tumor cells, most likely due to lack of perpancreatic soft tissue in this area, Yeo et al showed in their series of 201 patients that the 5 year survival in those with I negative margin was 26% (median survival 12 months) compared to those with a positive margin 8% (median survival 10 months)^[12].

While margin positivity appear to be critically important, not all margins may have a similar impact on patient survival. Delperio et al reported that positive SMA or SMV margin had a significant impact on progression-free survival, a positive posterior margin had no impact^[13]. In our study, two cases were retroperitoneal margin positive and one case was SMV margin positive. Two(4.4 %) of the cases suspected of malignancy in our study turned out to be benign on histopathology. They were Microcystic shroud cystadenoma and Acinar Cell Cystadenoma. One case (2.2%) was found to be non-neoplastic (cystic dystrophy of heterotropic pancreas in duodenal wall). Studies have shown the incidence of benign histopathology on PD specimens could be as high as 13%^[14]

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 pathological assessment in 24 cases(5%)^[15], VanGulik et al. described 220 patients who underwent Whipple procedure and reported 6% benign findings. They suggested that at least 5% of benign findings is expected when performing PD for a suspected malignant case (Table 12).

CONCLUSION

Pancreaticoduodenectomy (PD) specimen requires meticulous histopathological evaluation for proper categorisation of histopathological types and other features which affect patient survival following PD. Possibility of a benign diagnosis remains in PD specimens which have been resected presuming malignancy based on clinical judgement and radiological data.

The result found in our study were:

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- Out of it. 41 were malignant, 3 were benign and 1 was non-neoplastic.
- Youngest case was 21 years old and oldest case was 70 years. Mean age was 51.42 years with 2: 1 male predominance.
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- One case of PanNET was functional and show histology of Somatostatinoma. It was the known case of Neurofibromatosis I and patient had multiple well defined skin nodules. In the specimen multiple nodule were found in small intestine and it show histology of Gastro intestinal stromal tumor
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- 35(85.3%) cases were PDAC and Moderately differentiated Adenocarcinoma(58.7%) was most common histological type.
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