Original Article

# Analysis of Whipple's Resection Specimens: A Histopathological Perspective

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## ABSTRACT

**Background:** Pancreaticoduodenectomy or Whipples's procedure is done for pancreatic carcinoma, bile duct carcinoma, duodenal carcinoma and periampullary carcinoma. About 5% of the gastrointestinal malignancy is constituted by the ampullary and periampullary carcinoma. Histopathological studies related to the diagnosis, grade, stage, nodal status, marginal status, prognosis and incidence of these tumors are analyzed from the received Whipple's specimen in our study. Aim of this study is to analyze the incidence of various tumors we encounter in the Whipple's specimen, to calculate the sex ratio, to grade and to stage the tumors based on the WHO grading system. And to compare the incidence with other studies.

**Methods:** Histopathology records of all the patients who had Whipple's resection during September 2013 - September 2015 were analyzed. The slides were reviewed and the parameters were calculated.

**Results:** Out of thirty cases, on which Whipple's resection was done, twenty one had ampullary and periampullary carcinoma, The mean age incidence of ampullary carcinoma calculated was 44 years. The sex ratio of ampullary carcinoma was 1:1. Three had pancreatic tumors and six had chronic pancreatitis. Out of the three cases with pancreatic tumor, two had pancreatic endocrine tumors. They both were female. One had a Solid pseudopapillary pancreatic tumor. Literatures were reviewed and the predominance of ampullary carcinoma was noted in our study in contrast to other studies.

**Conclusion:** In the analysis of the Whipple's specimen we found out that ampullary adenocarcinoma predominates and there were an equal sex incidence. This is in contrast to other published literatures. This variable needs further evaluation.

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## Introduction

Pancreatoduodenectomy otherwise called Whipple's surgery was first demonstrated by Allen. O Whipple in 1935.[1] This procedure is done for 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. [2] 80% of the tumors in this region are adenocarcinoma and other malignancies form the rest. Ampullary carcinoma has the histological features of duodenal mucosa and the ducts. Tumors in this region are mostly seen among elderly age group around seventh decade and surgery is the only means of curing them. Because of the intimate location of many structures in this area even a benign lesion can cause obstructive symptoms. [2] Whipple's surgery had been done on those benign conditions as they mimick malignancy. Histopathology is the gold standard when such situation arises.

This study was done to analyze these Whipple's specimens histopathologically by retrieving the old records and slides and critically analyze and sort them according to the site, size, type, and grade, nodal and marginal status. Along with that, the age and sex incidence was analyzed. The prognostic significance of all these characters was analyzed to get the overall picture of these cases in our hospital setup. Comparison of the incidence of our hospital with other literatures was also attempted.

## Materials and Methods

This is a retrospective study of the cases done during September 2013- September 2014. All the cases on which Whipple's surgery was done for both the malignant and nonmalignant reasons were retrieved from the old records. The details about the gross examination of the specimen were taken from the records.

**Protocols used in the gross examination:**

- When most part of the tumor is located in the ampullary region and bulges into the duodenal mucosa stretching it, it is taken as ampullary carcinoma. Adsay V et al in their study had mentioned that they designate ampullary carcinoma if more than 75% of the tumor was seen in the ampullary region.[3]
- A tumor that involved the circumference of the ampulla was taken as periampullary carcinoma.
- A tumor that involved the circumference of the common bile duct [CBD] was taken as common bile tumors. Longitudinal thickening of the bile duct and granular mucosal surface were taken as clues. Gonzalez RS et al in their study had mentioned that common bile duct tumor constitutes 5% among the tumors of pancreatoduodenal origin. [4] The incidence of CBD tumor is higher among Asians.[3]
- A tumor with the base or the epicenter in the duodenum and not involving the ampulla was taken as duodenal carcinoma. Non ampullary duodenal carcinoma is different from its duodenal counterpart and the plaque like growth of the non ampullary carcinoma is associated with microsatellite instability. [5]
- Other gross features like cystic neoplasms of the duct, spongy areas in serous cystadenoma of the pancrea were noted.
- Tumor size, color, consistency, gross invasion and measurements were noted.
- Nodes- Number and size were noted.
- Homogenous white gross appearance was taken as a clue for pseudo tumors. Most of the benign lesion occurs around the pancreatic head and the periampullary region. They cause obstructive symptoms mimicking carcinoma leading on to Whipple's surgery.[2]

The slides were reassessed. Histopathological categorization, grading, tumor budding, staging, nodal status, perineural invasion, angioinvasion and marginal status were assessed.

The grading of adenocarcinoma was done based the percentage of glands seen in the tumor tissue. If there were >95% glands it was taken as well differentiated, 50-95% glands as moderately differentiated grade, 5-49% as poorly differentiated grade and ,5% as undifferentiated adenocarcinoma.

The staging of the Ampullary carcinoma was based on AJCC TNM classification.T1 – If the tumor is limited to the ampulla or sphincter of Oddi. T2- If the tumor invades the duodenal wall.T3- If the tumor invades the pancreas and T4- If the tumor invades the peripancreatic soft tissue or adjacent structures.N1- If there is regional nodal metastasis. In the case of Endocrine neoplasm, the following staging was followed. T1- If the tumor is limited to the pancreas and it is less than 2cm in diameter. T2 -If the tumor is restricted to the pancreas and size is between 2-4 cm. T3 - If the tumor is more than 4 cm diameter if it is limited to the pancreas or if the tumor invades the duodenum or the bile duct. T4- If the tumor invades the adjacent organs. N1- If the regional nodes are involved by the tumor. In case of the solid pseudo papillary tumor T1- When the tumor is limited to the pancreas and was less than 2cm in diameter.T2- When the tumor is limited to the pancreas and more than 2cm in diameter. T3- When the tumor invades duodenal, peripancreatic tissue and the bile duct. T4- When the tumor invades the other structures.

N1a- When a single node is involved. N1b- Multiple regional nodes were involved.

## Result

Thirty Whipple's specimen was received during our study period. Out of that, twenty one had ampullary carcinoma and periampullary carcinoma. It constitutes around 70% of the tumors in our study. When the age incidence of ampullary carcinoma was calculated the mean age of occurrence in our study was 44 years [Table 1]. The youngest case in our study was a 35 year old female. Neither familial clustering nor familial syndromes were seen in our study. When the sex ratio was analyzed among the patients with ampullary carcinoma, the male to female ratio in our study group was almost 1:1 [Table 1].

The mean size of the ampullary tumor in our study was 2.4cm [Table 2]. In 89.5% of the cases of the ampullary carcinoma was of intestinal type [Fig1] and 10.5% of the cases were of pancreatobilliary type [Fig 2]. Among them, 38% of the cases were well differentiated grade and 62% were moderately differentiated grade. Poorly differentiated grade was not observed in our study [Table 3].

In our study, 68% were in stage two [Table4]. Only 10% of the cases showed metastatic deposits in the nodes and 10% of the ampullary carcinoma showed angioinvasion [Fig 3] [Table 5]. Margins were free of tumor invasion in all the cases.

Pancreatic endocrine tumor was the second commonest tumor we encountered while analyzing the Whipple's specimen. In our study, both the cases with the pancreatic endocrine tumor were females [Fig 4]. They were 40 and 42 years old with the mean age of 41 years. Both the tumor was more than 2cm and they were in stage T2 [Table 2]. Both were nonfunctional and showed angioinvasion and neural invasion [Fig 5]

Whipple's surgery done in six cases presumed of malignancy was diagnosed as chronic pancreatitis in our study.

**Table 1: Age and Sex distribution**

| Lesions | 35-40 Years | 41-50 Years | 51-60 Years | 61-70 Years | >70 Years | Male | Female |
|---|---|---|---|---|---|---|---|
| Ampullary Carcinoma | 3 | 8 | 3 | 2 | 3 | 9 | 10 |
| Periampullary Carcinoma | - | - | 1 | 1 | - | - | 2 |
| Pancreatic Endocrine Tumor | 1 | 1 | - | - | - | - | 2 |
| Solid Pseuopapillary Tumor | 1 | - | - | - | - | - | 1 |
| Chronic Pancreatitis | - | - | 2 | 2 | - | 2 | 4 |

**Table 2: Tumor size distribution in the Whipple's specimen**

| Tumors | 1-2cm | 2.1-3cm | 3.1-4cm | >4.1cm |
|---|---|---|---|---|
| Ampullary carcinoma | 9 | 7 | 2 | 1 |
| Periampullary carcinoma | 1 | - | 1 | - |
| Pancreatic Endocrine Tumor | - | 1 | 1 | - |
| Solid Pseudo Papillary tumor | - | - | 1 | - |

**Table 3: The distribution of type and different grades among the ampullary carcinoma**

| Type | Well Differentiated grade | Moderately differentiated grade | Poorly differentiated grade |
|---|---|---|---|
| Intestinal | 8 | 9 | - |
| Pancreatobilliary | - | 2 | - |

**Table 4: Distribution of stages in Ampullary carcinoma [No. Of Cases]**

| T1 | T2 | T3 | T4 | N1 |
|---|---|---|---|---|
| 3 | 13 | 3 | - | 1 |

**Table 5: Angioinvasion, Neural invasion and Nodal status**

| Tumors | Angio Invasion | Neural Invasion | Nodal status | |
|---|---|---|---|---|
| | | | Reactive | Tumor deposits |
| Ampullary | 2 | - | 6 | 1 |
| Peri Ampullary | 1 | - | - | - |
| Endocrine | 1 | 1 | 2 | - |
| Solid Pseudo papillary tumor | 1 | - | 1 | - |

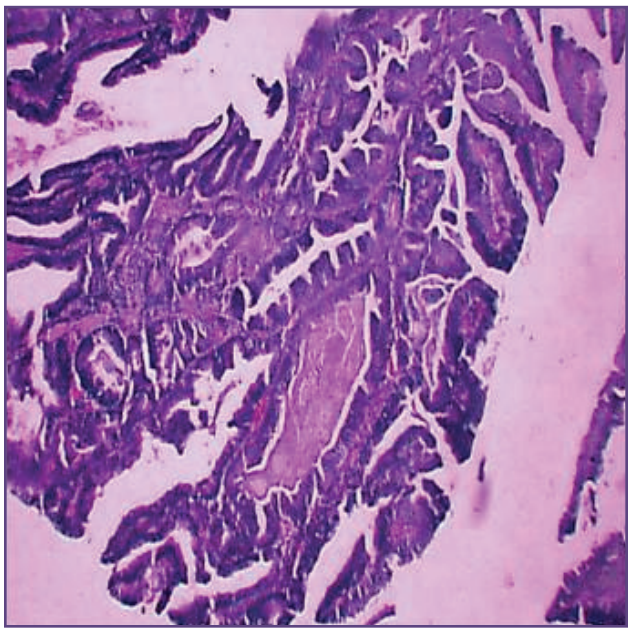


**Fig. 1: Shows tumor cells arranged in villoglandular pattern – Ampullary carcinoma – Intestinal type [10x H&E].**

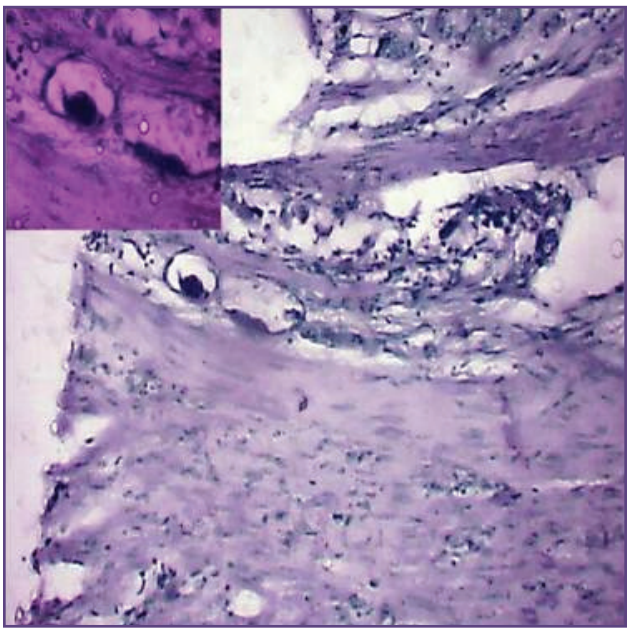


**Fig. 3: Shows angioinvasion in ampullary carcinoma [4x H&E] Inset shows a closer view [40x H&E].**

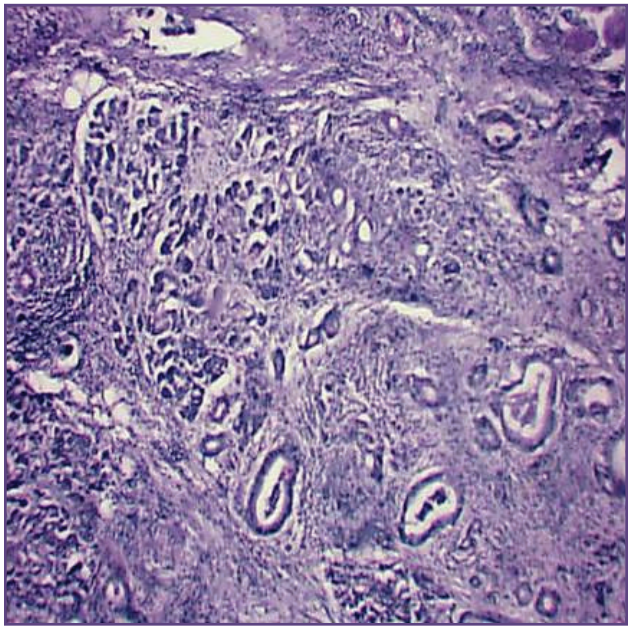


**Fig. 2: Shows Pancreatobilliary type of ampullary carcinoma in which tumor cells are arranged in a glandular pattern in a desmoplastic stroma infiltrating the pancreas [4x H&E]**

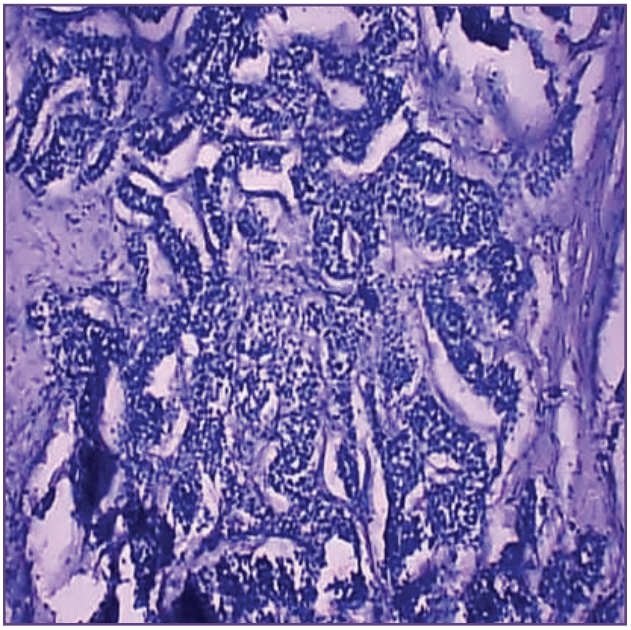


**Fig. 4: Shows endocrine tumor of the Pancreas in which the tumor cells are arranged in cords, nests and trabeculae [4x, H&E].**

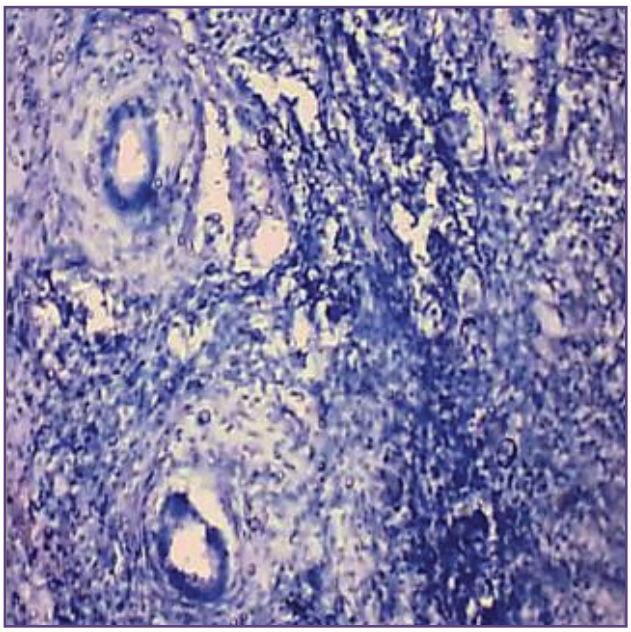
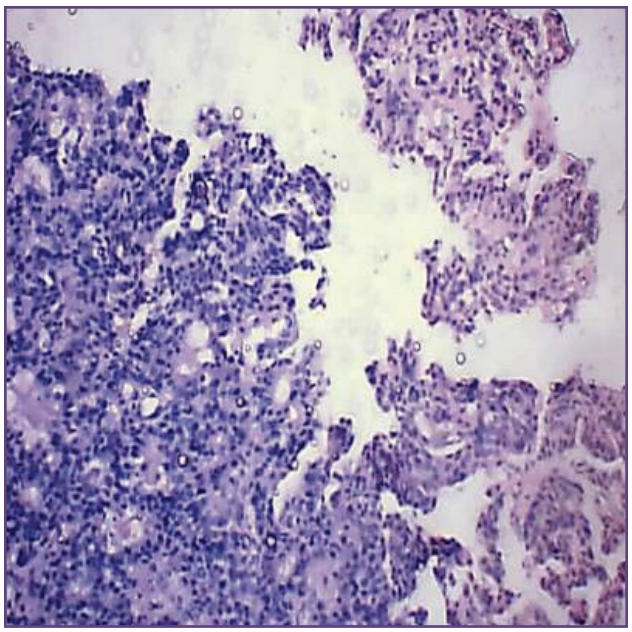


**Fig. 5: Shows neural invasion [10x H&E].**



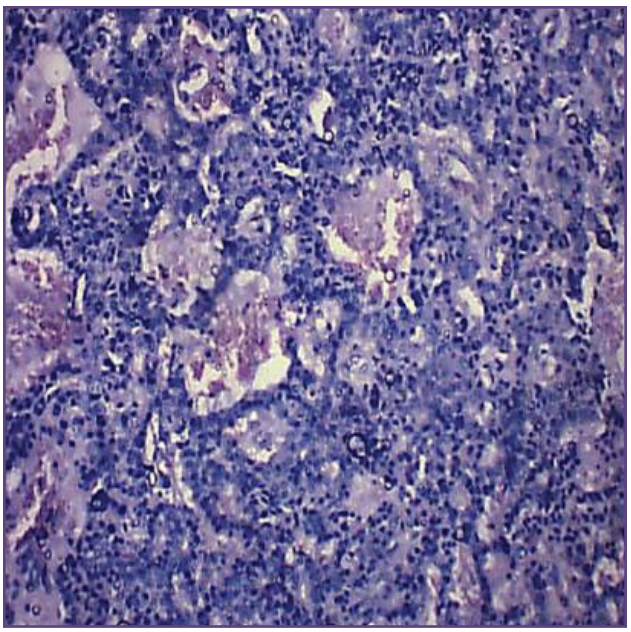


**Fig. 6&7: Shows tumor cells arranged around the blood vessels and in some areas they show pseudopapillary arrangement-Solid Pseudopapillary tumor [10x and 40x respectively H&E].**

## Discussion

Whipple's surgery is done for the tumors involving the ampullary region, periampullary region, common bile duct, duodenum and the pancreas and its ducts. Ampullary region as such is 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 insitu involvement from the invasive ampullary carcinoma is difficult for the young pathologists. Lobular glandular architecture with lamina propria surrounding the glands, the rounded glands and absent stromal response are the clues to rule out the invasive component when such dilemmas arise.

In our study ampullary carcinoma was more prevalent among the Whipple's specimen [70%]. According to Saraee et al and Landis S H et al, pancreatic adenocarcinoma was most common among the Whipple's specimen in the western population.[1, 6] Ampullary carcinoma constitutes 16-20% of all the carcinomas of the periampullary region, according to Duffy et al, Talamini et al and Howe et al which is contrast to our study. [7-9]

Ampullary adenocarcinoma constitutes about 0.2% of all the gastrointestinal tumors. [10] It constitutes 6% among the tumor of the periampullary region. [9] It is associated with Familial Polyposis syndrome and neurofibromatosis and K ras mutation.[11-14] Klimstra et al had proposed the diagnostic criteria for ampullary carcinoma.[15] According to them, the tumor should be called as ampullary when the epicenter is in the ampulla and there should be a pre invasive lesion in the ampulla. The tumor that grows circumferentially around the ampulla is called periampullary carcinoma. Ampullary tumors are predominantly seen in males in their seventh decade. Henson et al in their study had mentioned that the age incidence of ampullary carcinoma was 69.7 years. [16] Howe et al in their study had mentioned that mean age incidence in their study was 65.6 years. [9] The youngest case in Howe et al's study was 28.3 years old with a history of familial adenomatosis syndrome.[9] In Yeo JC et al's study, the mean age of occurrence was 64 years with a male predominance.[17] In contrast, the mean age incidence in our study was 44 years and there was equal sex incidence. Yeo JC et al in their study had mentioned that tumor diameter was smaller for ampullary carcinoma [17] In Howe et al's study, mean size of the ampullary tumor was 2.7cm which correlated with our study.[9]

Histopathologically, the ampullary carcinoma can be of intestinal type, pancreatobilliary type, mixed type and undifferentiated type. Categorization is important because the prognosis of the intestinal type is better than pancreatobilliary type. [18] 66% of ampullary carcinoma seen in Howe et al's study was of intestinal type and 27% was of pancreatobilliary type which is in correlation with our study.[9] In their study well and moderately differentiated graded tumors predominated as seen in our study.[9] According to Yeo JC et al's study, well differentiated tumors were uncommon.[17] The nodal involvement was 10% in our study. In contrast, the nodal metastasis ranged from 29% to 52% in Warren KW et al's study and 40% in Allema JH et al's study. [19,20]

Carcinoma mimics include adenomyoma of the ampulla, papillary hyperplasia, sclerosing papillitis and anatomic pancreatitis. The adenomyoma or adenomyomatous hyperplasia of the ampullary is larger than 0.5cm and contains complex glands, arranged in a lobular architecture surrounded by the lamina propria and muscle bundle. Its presentation in the elderly individual and its obstructive symptoms may point towards malignancy, but it is distinguished by its architecture and lack of dysplasia and mitosis. [21,22]

Other differential includes papillary hyperplasia. Again, this one also lacks atypia and it is an incidental finding and does not produce any symptoms. But when papillary hyperplasia is secondary to cholelithiasis or ampullary inflammation, then reactive atypia may be seen mimicking carcinoma. Sclerosing papillitis is associated with IgG4 group mediated autoimmune disorder. It causes swelling in the ampullary region. [23] Marked atypia seen in the duodenal mucosa surrounding this lesion can mimic carcinoma. Paraduodenal pancreatitis otherwise called anatomical pancreatitis is another symptomatological mimicker for ampullary carcinoma. It causes obstructive symptoms and it is common in the middle aged alcoholic. [24]

Treatment for insitu carcinoma and micro invasive carcinoma of the ampullary region is transduodenal ampullectomy and Whipple's surgery is for the invasive tumors. [25] The prognosis of the ampullary carcinoma is better when compared with ductal carcinoma or pancreatic carcinoma. [26,27] Other prognostic indicators are the stage of the disease, tumor budding, margin free status, MIB index, invasion and DNA ploidy. [28-30] In Howe et al's study, size more than 2cm, pancreatobilliary type, perineural invasion, angioinvasion, positive margins and positive nodal involvement were associated with decreased in the median survival rate. [9]

The incidence of pancreatic endocrine tumor is 5.25/100 000/year. [20] The incidence of pancreatic endocrine neoplasm is less than 3% of all the pancreatic neoplasms according to Henson et al. [16] They have also

mentioned that ductal carcinoma is more common among the pancreatic neoplasm. But in our study, we did not come across a single pancreatic ductal carcinoma. Mean age of pancreatic endocrine tumors was 55 – 60 years and younger age incidence are associated with MEN syndrome and VHL disease according to Oberg et al. [31] Male predominance was seen according to Oberg et al. [31] It may be a functional or nonfunctional tumor and the majority is nonfunctional. The prognosis of the nonfunctional tumor was inferior according to Halfdanarson et al. [32] Histologically, it is composed of uniform round cells with dispersed chromatin arranged in nests, trabeculae and in festoons. Psammoma bodies and amyloid like material are seen. Mitosis are less than 10/HPF and there is no necrosis in well differentiated tumors. Worst prognostic factors include poor differentiation, extremes of age, functionality, increased size, metastasis, necrosis, increases mitosis, vascular and neural invasion, CD10 and CD19 expression. Resection is the treatment of choice. It is an indolent tumor with malignant potential. Compared with the adenocarcinoma of the pancreas, endocrine tumors have better prognosis. [32]

Solid Pseuopapillary tumor is a tumor of the young female and middle aged women. Patel et al in their study had mentioned that this tumor is prevalent in young female with the median age of 20 years. [33] Martin RC et al in their study had mentioned the medial age as 39 years, which correlated with our study. [34] It is a cystic and solid neoplasm involving the head and tail of the pancreas. Histopathologically, this tumor has an appearance of the endocrine neoplasm composed of small round cell crowding around the blood vessels. The extensive necrosis of the cells that are away from the blood vessels gives it a pseudo papillary appearance. Individual cells are smaller with oval and folded nucleus. Mitosis is few in number. This tumor expresses beta catenin, Vimentin, CD10 and CD56. [35] This is a tumor of intermediate malignant potential with frequent metastasis to the liver. [33] For localized tumor surgery is the treatment and for metastatic tumors, aggressive management is required.

Six cases were diagnosed as chronic pancreatitis on the Whipple's specimen suspected as periampullary carcinoma. De la Fuente SG in their study had mentioned that in the Whipple's specimen they have received they have encountered 7% benign cases.[36] Endoscopic biopsies have limited diagnostic accuracy in case of ampullary carcinoma. [37] FNAC and other investigative modalities have limited application in accurately diagnosing the tumors in this area because of the complex and intimate anatomy of the ampullary area. [2]

When the incidence of various carcinomas diagnosed on the Whipple's specimen by us was compared to Yeo et al, Chan C et al and Michelassi et al's study pancreatic ductal carcinoma were more prevalent in their study groups in contrast to our study. [17, 38, and 39] [Table 6]. The age incidence of their study groups was around 65 years. But in our study it was 44 years. Equal sex incidence was noticed in our study in contrast to the male predominance in their study. This may be due to the difference in the genetic makeup or other etiological factors which needed further studies.

## Conclusion

As we analysed the Whipple's specimens, many questions were raised. All the reviewed literatures had mentioned that pancreatic ductal carcinoma as the commonest tumor in the periampullary area. But ampullary carcinoma was predominant in our study. Ampullary carcinoma was seen in a relatively younger age group than the global age incidence and there was an equal sex incidence in contrast to the literature reports of male predominance. Surprisingly, pancreatic ductal carcinoma was not seen in our study. More studies are needed to analyze the genetic makeup, dietary or environmental factors among our people that are responsible for this contrast.

## Acknowledgements

## Funding

None

**Table 6: A Comparative analysis of our study with other's studies**

| Studies | Ampullary carcinoma-Intestinal type | Ampullary carcinoma-Pancreatobilliary type | Duodenal carcinoma | Bile duct carcinoma | Pancreatic ductal carcinoma | Solid Pseudo Papillary tumor | Pancreatic Endocrine tumor | Benign lesions | Median age | Sex predominance |
|---|---|---|---|---|---|---|---|---|---|---|
| Our study | 63% | 6.7% | - | - | - | 3.3% | 6.7% | 20% | 44 years | Equal sex ratio |
| Howe et al[9] | 76% | 27% | - | - | - | - | - | - | 65.6 years | Male |
| Yeo et al[17] | 19% | - | 7% | 12% | 62% | - | - | - | 64 Years | Male |
| Chan C et al[38] | 76% | - | 3% | 5% | 15% | - | - | - | 65 years | Male |
| Michelassi F et al[39] | 4.3% | | 2.5% | 6.2% | 85% | - | - | - | 60.5 years | Male |

## Competing interests

None

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