Original Research Article

Histopathological spectrum in Whipple's resection specimens – A six years retrospective study in a tertiary care centre

Abstract

Aims and Objectives : To study the demographic distribution and histomorphological variations of Whipple's pancreaticoduodenectomy specimens in regard to tumour site, size, type, grade, marginal status, lymph node metastasis, perineural invasion (PNI) and lymphovascular invasion (LVI). This study will also highlight the incidental pathological lesions occurring in Whipple's specimens. Hence it will further facilitate to analyse the prognostic significance of all these parameters in order to co-relate the overall spectrum of these cases.

Study Design and Place of Study : An observational retrospective time bound descriptive study conducted at Indira Gandhi Institute of Medical Sciences (IGIMS), Patna after approval of ethical committee.

Material and Methods : A total of 150 Whipple's resection specimens received in the Department of Pathology, IGIMS, Patna from January 2015 to December 2020 were selected as per inclusion and exclusion criterias. Details were collected from histopathology request forms and hospital record sheets. Gross and microscopic features were analysed and recorded. Slides were reviewed and the parameters were calculated.

Results : Statistical analysis showed that out of 150 Whipple's pancreaticoduodenectomy specimens, 141 (94%) cases were malignant tumours, 6(4%) cases had low malignant potential and 3 (2%) cases were of benign nature. Periampullary carcinomas were the predominant malignant tumours (78.66%), followed by ampullary carcinomas (14%) and pancreatic endocrine tumours (1.33%). Tumours with low malignant potential were constituted by SPN (solid pseudopapillary neoplasm of the pancreas) (2.67%), GIST (gastrointestinal stromal tumours) (0.67%) and mucinous cystic neoplasm of the pancreas (0.67%). Mean age incidence was 49.57 years with a male to female sex ratio of 1.4:1. Most of the malignant

tumours (more than 75%) were moderately differentiated and were in stage2 category. Out of the total 141 malignant tumours, 71 (50.35%) cases showed LVI, 50 (35.46%) cases had PNI and 84 (81.67%) had tumour deposits in the lymph nodes.

Conclusions : Our study emphasizes the importance of tumour grade, tumour stage, presence of LVI, PNI, positive margins and lymph node metastasis as strong prognostic factors for patient survival. This is well corroborated by the significant P value in our study. Most of our cases were diagnosed at a locally advanced stage. Hence a more precise assessment and clinical evaluation can lead to early detection of cancer, improving the survival rates.

1. Introduction

The first successful local resection of a periampullary tumour was performed by Dr William Halsted in the year 1898.[1] This was followed by the regional resection of the duodenum and a part of the pancreas (pancreaticoduodenectomy) for the periampullary tumour in 1909 by Kaush and subsequently reported in 1912.[2] Further the procedure was modified by Allen Oldfather Whipple in 1935 by complete removal of the head of the pancreas and whole of the duodenum.[3] Brunschwig further extended the indications for pancreaticoduodenectomies to include pancreatic carcinomas in the year 1937.[4]

Currently Whipple's procedure (pancreaticoduodenectomy) is being done for tumours of the ampullary region, periampullary region, pancreas including the pancreatic duct, common bile duct (CBD) and duodenal area.[5] This procedure involves the removal of pancreatic head, part of duodenum, part of bile duct and the lymph nodes in the vicinity. Sometimes the gall bladder and part of stomach are also resected. Owing to the intricate arrangement of the organs in this area, occasionally even a benign lesion can produce obstructive symptoms mimicking malignancy.[5] In such situations histopathology is the gold standard.

Ampullary and periampullary carcinomas constitute about 5% of gastrointestinal malignancies, 80% of these being adenocarcinomas,[6] most commonly seen in the elderly group around seventh decade.[7,8] The anatomic intricacies has made pancreaticoduodenectomies one of the challenging surgeries. Advances in the surgical methodologies coupled with peri and post operative care has markedly improved the morbidity and mortality demographies.

Assessing the Whipple's specimen histopathologically is essential in evaluating the prognostic factors namely, tumour size, site, grade, extension, resection margin status, LVI, PNI, lymph node status and tumour staging.[9,10,11]

This study was undertaken to evaluate the demographic distribution and histopathological spectrum in pancreaticoduodenectomy specimens in a tertiary level hospital over a span of six years.

2. Materials and Methods

2.1 Study Design, Place of Study and Ethical Clearance

An observational retrospective time bound descriptive study was conducted at Indira Gandhi Institute of Medical Sciences (IGIMS), Patna after approval of ethical committee.

2.2 Data Collection and Time of Study

This study was done over a period of six years from Jan 2015 to Dec 2020. Details of all the cases which had undergone Whipple's resection were retrieved from the departmental archive of records, slides and blocks. 150 cases (including malignant and benign cases) were analysed in regard to age and sex distribution, tumour size, site and gross examination. Slides were reassessed for microscopic findings, tumour extension, resection margins, lymph node status, LVI, PNI, tumour grading and staging.

2.3 Criterias for Inclusion and Exclusion

Inclusion Criteria : All Whipple's resection specimens received in the Dept of Histopathology, IGIMS, Patna during the period of January 2015 to December 2020.

Exclusion Criteria : (i) Specimens with prior history of neoadjuvant treatment.
(ii) Whipple's resection cases received for slide review without gross specimens were excluded from the study.

2.4 Grossing protocols in regard to tumour location :

Ampullary tumours encompasses the tumours located in the most distal intraduodenal portion of common bile duct (CBD) and main pancreatic duct (MPD) as well as those located in the small protruberance of the duodenum (papilla of Vater) where the duct epithelium transitions into duodenal mucosa supported by a muscle bundle (sphinter of Oddi).[12] Carcinomas arising in the mucosa of the confluence of the pancreatic and CBD or in the epithelium covering the papilla of Vater were taken as ampullary carcinomas.[13] These tumours were further classified as intestinal and pancreatobiliary types based on the microscopic examinations. This categorization is important as the prognosis of intestinal variant is better than the pancretobiliary variety.[14]

Periampullary tumours are a heterogenous group of neoplasms arising from the pancreatic head, distal CBD and the duodenum. Hence periampullary tumours were taken as tumours located at the circumference of ampulla.[15]

Tumours involving the circumference of the CBD, including longitudinal thickening of CBD were considered as CBD tumours.[16]

Tumours with the base or epicenter in the duodenum with sparing of the ampulla were taken as duodenal tumours.[17]

Adenocarcinoma grading was done based on the percentage of glands seen in the tumour tissue.[18]

Well differentiated : Presence of >95% glands

Moderately differentiated : Presence of 50 to 95% glands

Poorly differentiated : Presence of 5 to 49% glands

Undifferentiated : Presence of <5% glands

TNM Staging was done as per 8th Edition AJCC Cancer Staging Manual.

2.5 Statistical Analysis

Using SPSS version 22, Chi square test was done for data analysis and P value was calculated. P value of <.05 was considered significant.

3. Results

150 patients underwent Whipple's pancreaticoduodenectomy surgery, during a period of six years (January 2015 to December 2020). 87 (58%) patients were males and 63 (42%) were females (Fig1). The mean age of the patient was 49.57 years (age ranging from 14 to 72 years). Most common age group was 41 to 50 years (Table1, Fig3) and the tumour was predominantly adenocarcinoma. The youngest case in our study was 14 year old female diagnosed with SPN. On analysis the sex ratio was 1.4:1.

Among the 150 specimens examined 141 (94%) comprised of malignant tumours, 6(4%) showed tumours with low malignant potential and 3 (2%) were of benign nature (Fig2). Periampullary carcinomas were the predominant malignant tumours (78.66%), followed by ampullary carcinomas (14%) and pancreatic endocrine tumours (1.33%). Tumours with low malignant potential were constituted by SPN (2.67%), GIST (0.67%) and mucinous cystic neoplasm of the pancreas (0.67%). Single case of pseudopancreatic cyst and 2 cases of chronic pancreatitis were seen, which were operated owing to the obstructive symptoms mimicking malignancy (Table1, Fig4).

The mean size of ampullary and periampullary tumour in our study was 2.2cm and 2.7cm respectively (Table2). Histopathologically all the ampullary and periampullary tumours were adenocarcinomas. 16 (76.19%) cases of ampullary carcinoma were of intestinal type and 5 (23.80%) cases were pancreatobiliary in nature. Among the intestinal ampullary carcinomas 4 (19.04%) cases were well differentiated (Image1) and 12 (57.14%) cases were moderately differentiated. 1 (4.76%) case of pancreatobiliary ampullary carcinoma was well differentiated and 4 (19.04%) cases were moderately differentiated. No ampullary tumour was found to be poorly differentiated in our study (Fig6). Among the periampullary carcinomas 92 (77.97%) had origin in the duodenum, 23 (19.49%) originated from the pancreas and 3 (2.54%) were located in the distal CBD. 23 (19.49%) cases of duodenal periampullary carcinomas were well differentiated, 67 (56.77%) were moderately differentiated (Image2) and 2 (1.69%) cases were poorly differentiated (Image3). 4 (3.38%) cases of pancreatic periampullary carcinomas were well differentiated, 18 (15.25%) cases

were moderately differentiated and only 1 (0.84%) case was poorly differentiated. 2 (1.69%) cases of periampullary CBD tumours were well differentiated, only1 (0.84%) was moderately differentiated and no case was classified as poorly differentiated (Fig7). Overall 5 (23.8%) cases of ampullary carcinomas categorized as well differentiated and 16 (76.19%) cases as moderately differentiated. No tumour fell in the category of poorly differentiated. Among the periampullary carcinomas 31 (26.05%) cases were well differentiated, 85 (71.42%) were moderately differentiated and 3 (2.52%) cases were poorly differentiated (Fig5).

Our study reflected 14 (66.67%) cases of ampullary carcinomas in stage2, 4 (19.04%) cases as stage3 and 3 (14.29%) cases as stage1 (Fig8).

Of the ampullary carcinomas 6 (28.57%) cases had LVI, 8 (38.09%) cases showed metastatic deposits in the lymph nodes and only 3 (14.28%) case depicted PNI. Among the periampullary carcinomas 65 (55.08%) cases showed LVI (Image4) with 76 (64.41%) cases showing tumour deposits in the lymph nodes (Image6) and 47 (39.83%) cases having PNI (Fig9,Image5). Distribution of LVI, PNI and lymph node metastasis using Chi square test is depicted in Table3 showing a significant P value. Only one case in totality showed involved resection margin.

The third commonest tumour of our study was SPN of the pancreatic head with 4 cases, 3 occurring in females and 1 in male. All the 4 cases were less than 25 years with the mean age of 18 years. The mean size was 6.75cm (range 5 to 10cm).

Our study encountered 2 cases of pancreatic endocrine tumours, located in the head of the pancreas and both occurring in females having respective age of 39 and 47 years, giving a mean age of 43 years. Maximum diameter of the tumours were 2 and 2.4cm respectively with a mean of 2.2cm. Both these tumours were well differentiated and were categorized as low grade and intermediate grade respectively. The tumours were non functional and did not show LVI, PNI or lymph node metastasis.

We had one case of duodenal GIST in a 62 year male. The maximum tumour dimension was 5.5cm and was histopathologically categorized as low risk grade. LVI, PNI and lymph node metastasis were absent.

We came across a single case of Mucinous cystic neoplasm of the pancreas in a 46 year old female, having a maximum tumour dimension of 3.7cm. Microscopically it was classified as non invasive in nature. LVI, PNI and lymph node metastasis were characteristically absent.

The common post surgical complications encountered in our study were wound infections (19.3%), followed by pancreatic leak (18.6%) and delayed gastric emptying (14.6%) (Table4). 6% cases had postoperative bleeding which were managed conservatively. 4% (6patients) had to undergo resurgery as three developed severe haemorrhage, two had obstruction and one incurred intra abdominal abscess. Bile leak was observed in 2% cases. The early post operative mortality group (death within 30days from surgery) was 4% (6cases). The cause of death was septic shock in three cases, massive gastrointestinal bleeding in two cases and one patient developed pulmonary thromboembolism.

Table 1 : Age and Sex Distribution of Cases

Diagnosis	10 – 20 years	21 – 30 years	31 – 40 years	41 -50 years	51 – 60 years	61 years & above	Male	Female
Ampullary Carcinoma	Nil	1	4	5	8	3	13	8
Periampullary Carcinoma	Nil	Nil	19	41	29	29	70	48
Pancreatic Endocrine Tumour	Nil	Nil	1	1	Nil	Nil	Nil	2
Gastro Intestinal Stromal Tumour (GIST)	Nil	Nil	Nil	Nil	Nil	1	1	Nil
Solid Pseudopapillary Neoplasm of the pancreas (SPN)	2	2	Nil	Nil	Nil	Nil	1	3
Mucinous Cystic Neoplasm of the pancreas	Nil	Nil	Nil	1	Nil	Nil	Nil	1
Pseudopancreatic Cyst	Nil	Nil	Nil	1	Nil	Nil	1	Nil
Chronic Pancreatitis	Nil	Nil	2	Nil	Nil	Nil	1	1

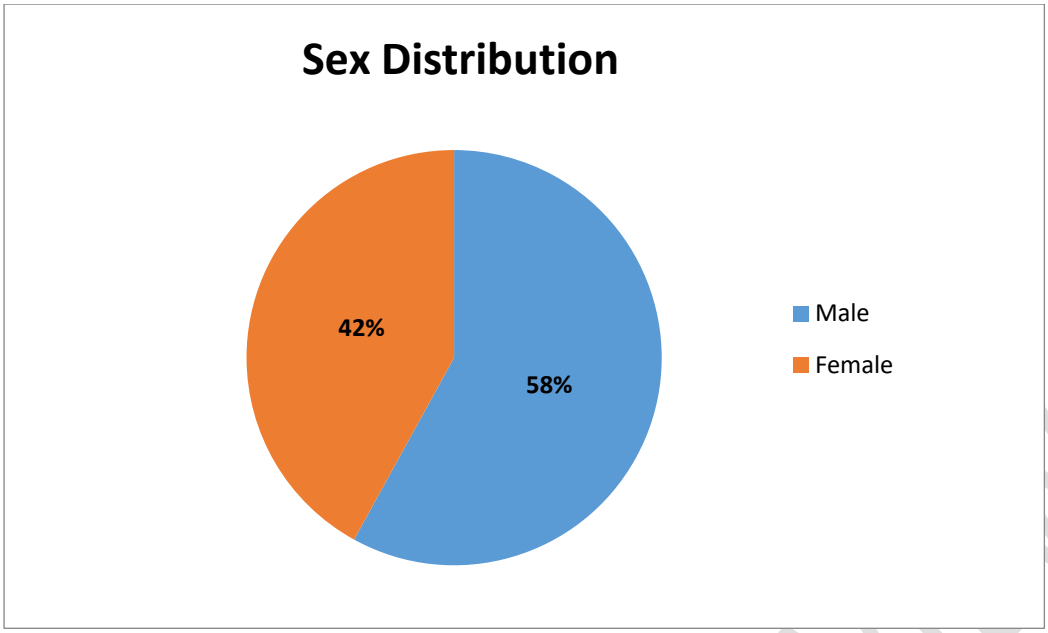

Fig 1 : Sex Distribution of Pancreaticoduodenectomy specimens

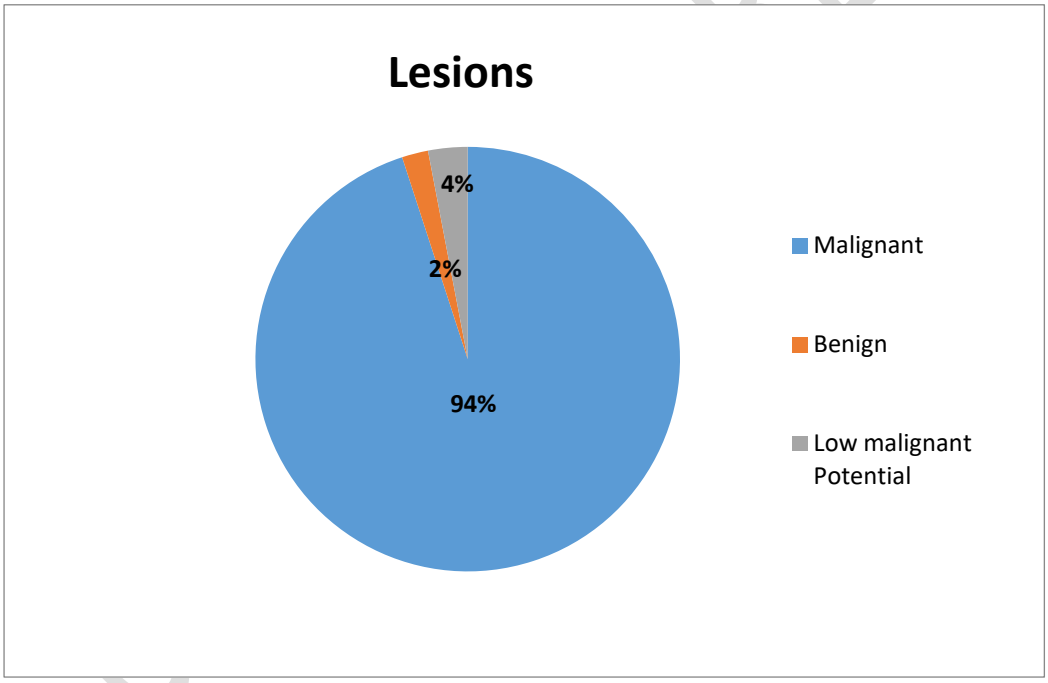

Fig 2 : Case Distribution as per Tumour Malignancy Potential

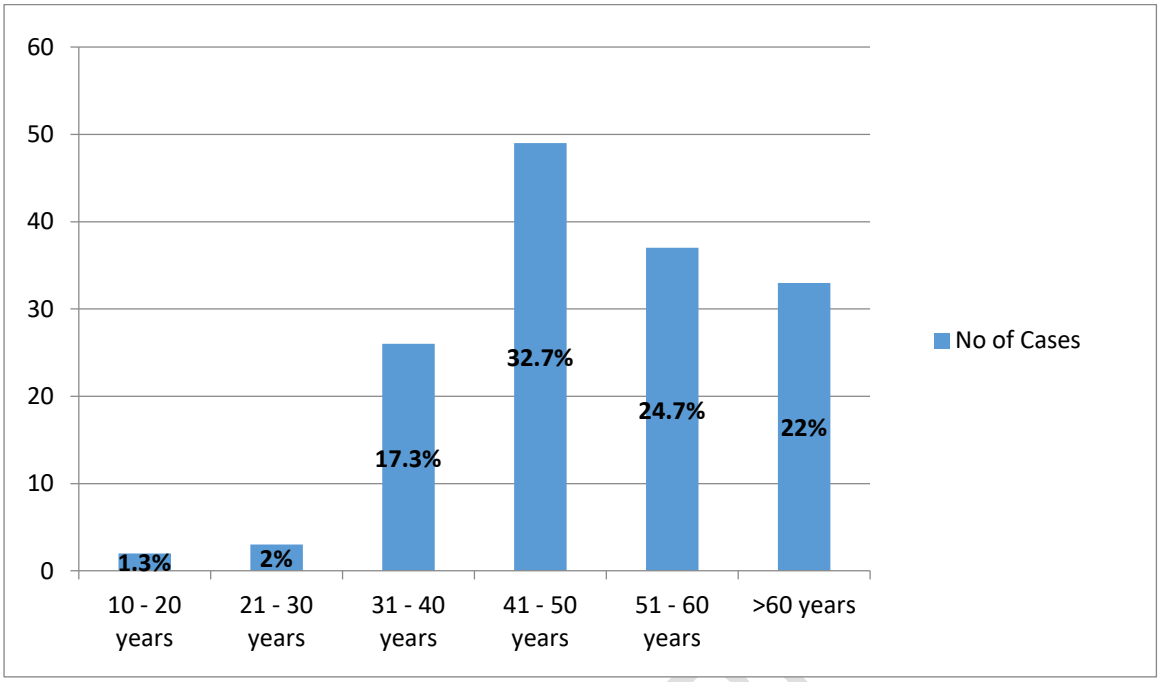

Fig 3 : Age wise patient distribution undergoing Pancreaticoduodenectomy

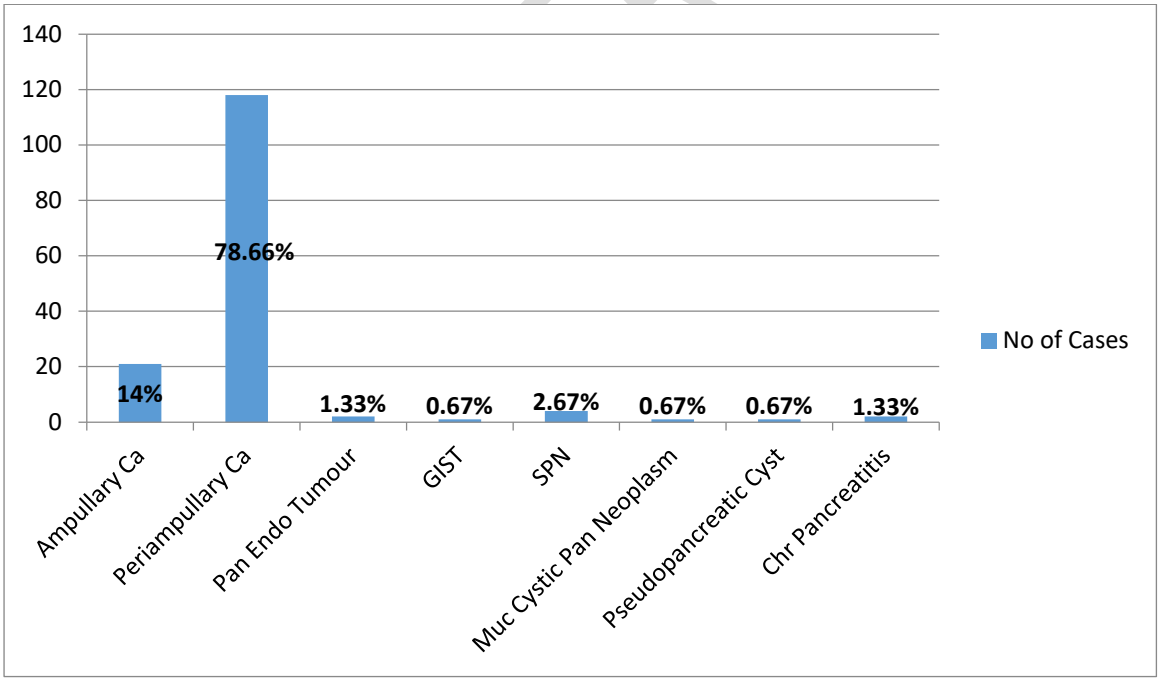

Fig 4 : Histopathological distribution of cases post Pancreaticoduodenectomy

Table 2 : Tumour size distribution in Pancreaticoduodenectomy specimens

Diagnosis	<1cm	1 - 2cm	2.1 – 3cm	3.1 – 4cm	>4.1cm	Mean Size(cm)
Ampullary Carcinoma	-	9	8	3	1	2.2
Periampullary Carcinoma	2	47	56	11	2	2.7
Pancreatic Endocrine Tumour	-	1	1	-	-	2.2
Gastro Intestinal Stromal Tumour (GIST)	-	-	-	-	1	-
Solid Pseudopapillary Neoplasm of the Pancreas (SPN)	-	-	-	-	4	6.75
Mucinous Cystic Neoplasm of the Pancreas	-	-	-	1	-	-
Pseudopancreatic Cyst	-	-	1	-	-	-
Chronic Pancreatitis	2	-	-	-	-	-

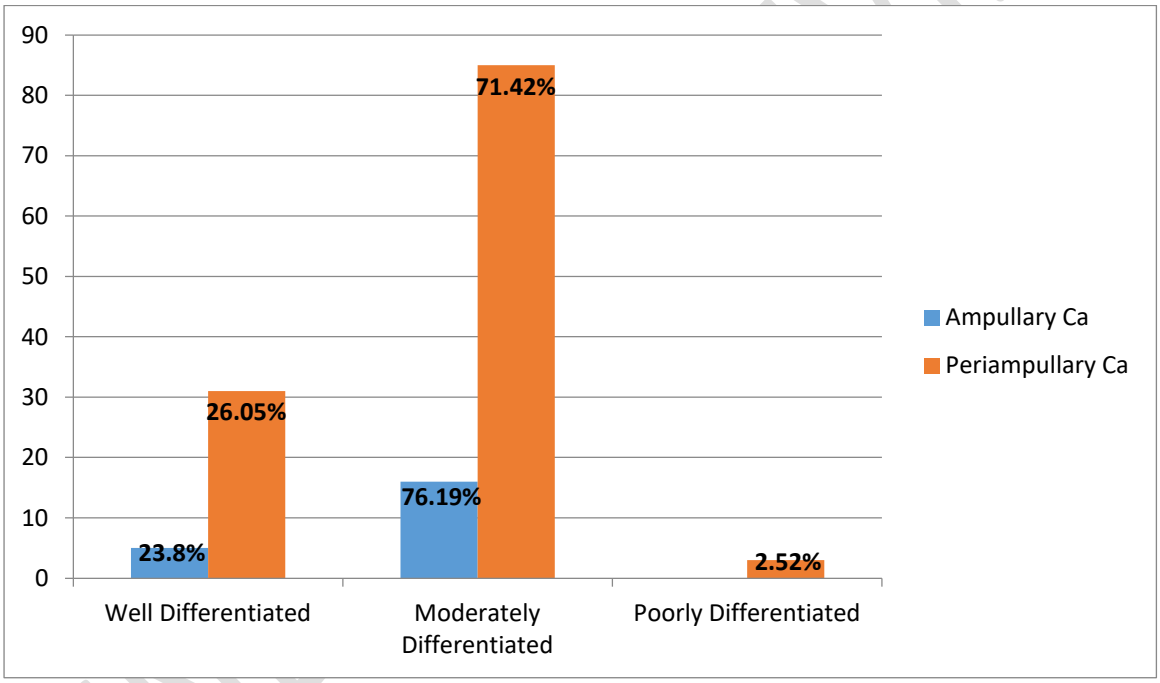

Fig 5 : Tumour grade distribution

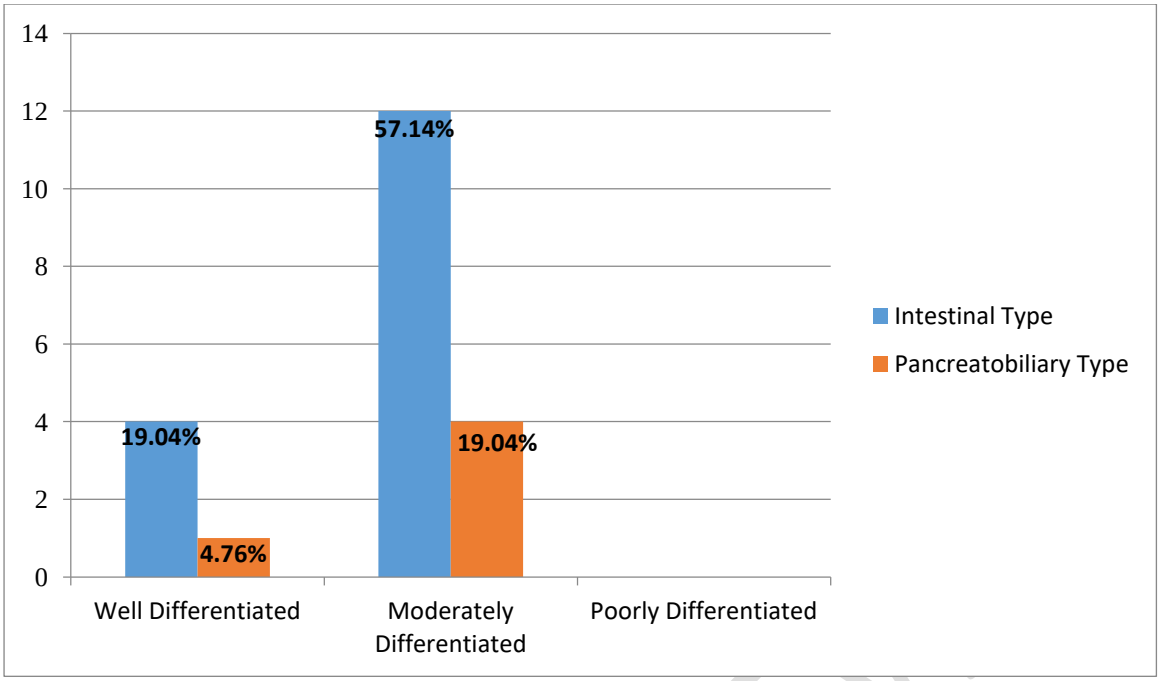

Fig 6 : Tumour grade distribution among Ampullary Carcinomas

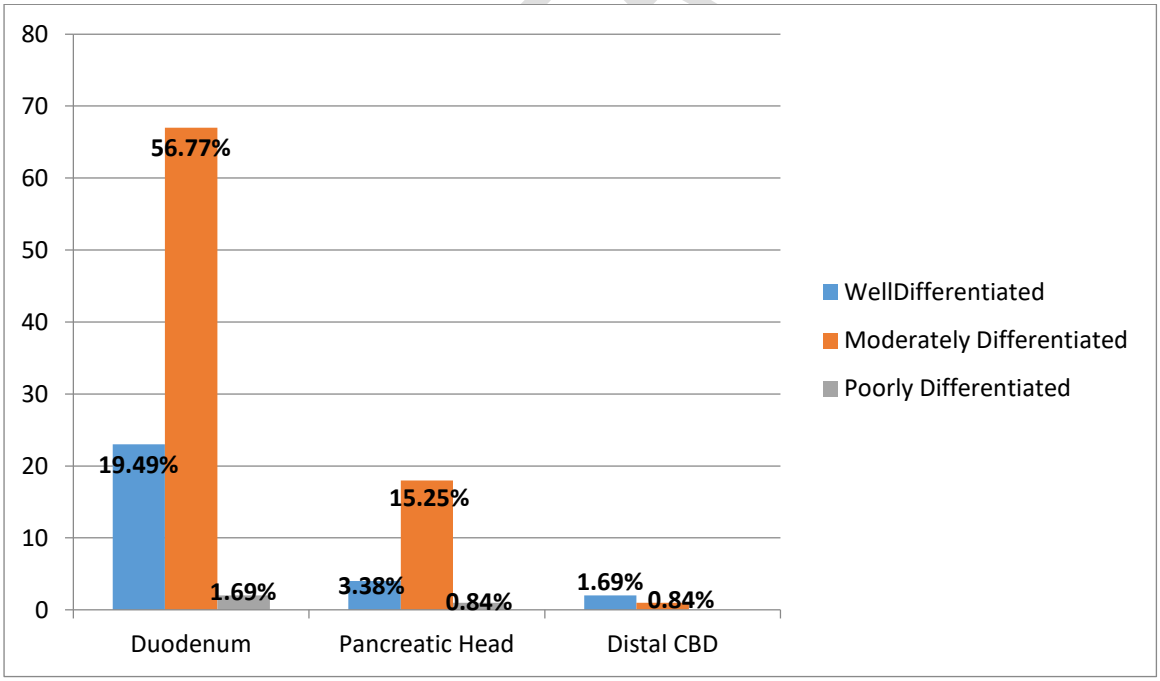

Fig 7 : Tumour grade distribution among Periampullary Carcinoma based on site of origin

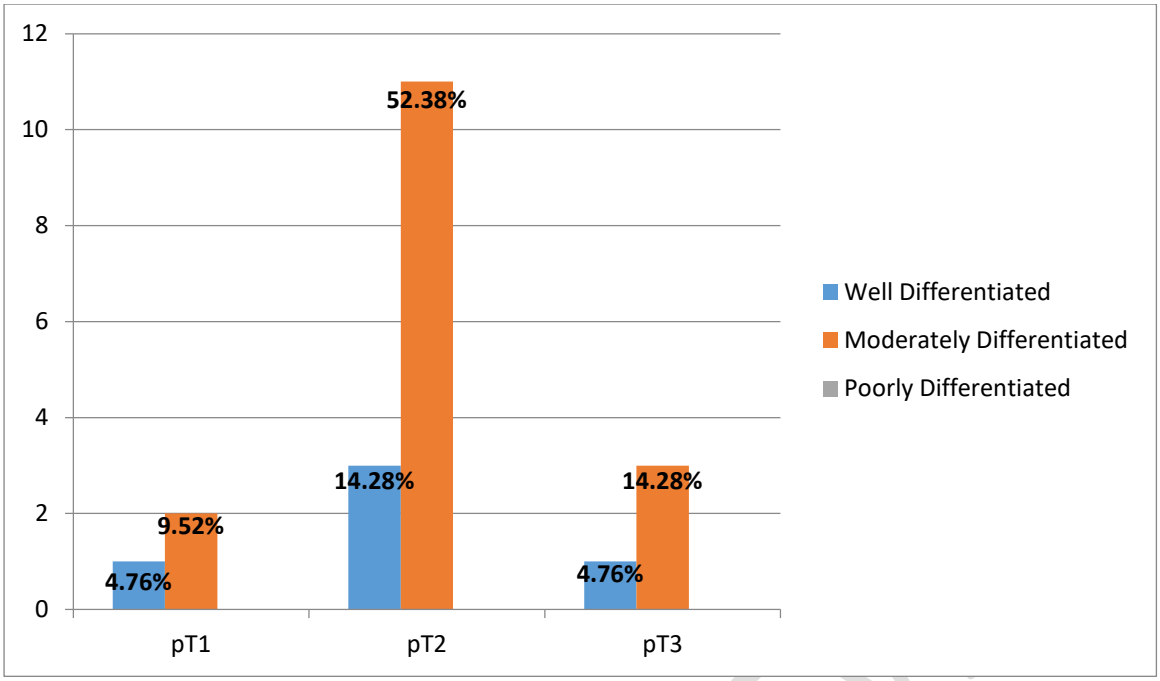

Fig 8 : **Distribution of Pathological Staging of Malignant Tumours**

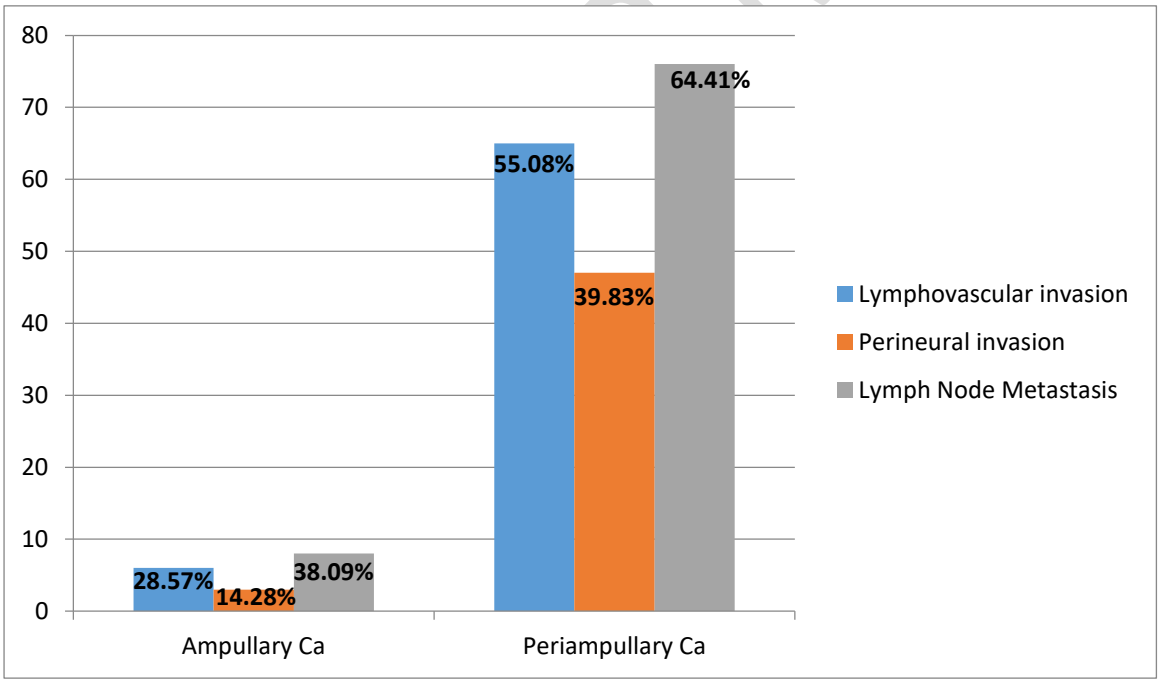

Fig 9 : **Lymphovascular invasion, Perineural invasion and Lymph Node Metastasis**

Table 3 : **Chi Square Results**

Tumour Type	**LVI Present**	**LVI Absent**	**Chi Square Test**	**P Value**
Ampullary Carcinoma	6	15	5.015	.025
Periampullary Carcinoma	65	53		
	PNI Present	**PNI Absent**		
Ampullary Carcinoma	3	18	5.050	.024
Periampullary Carcinoma	47	71		
	LN Metastasis Present	**LN Metastasis Absent**		
Ampullary Carcinoma	8	13	5.161	.023
Periampullary Carcinoma	76	42		

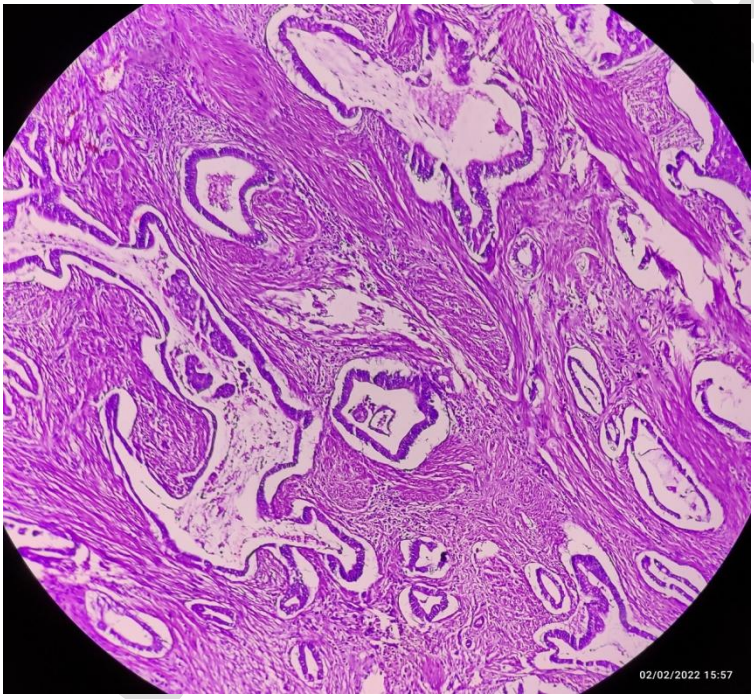

Image1 : H&E (40x)Well differentiated intestinal ampullary adenocarcinoma

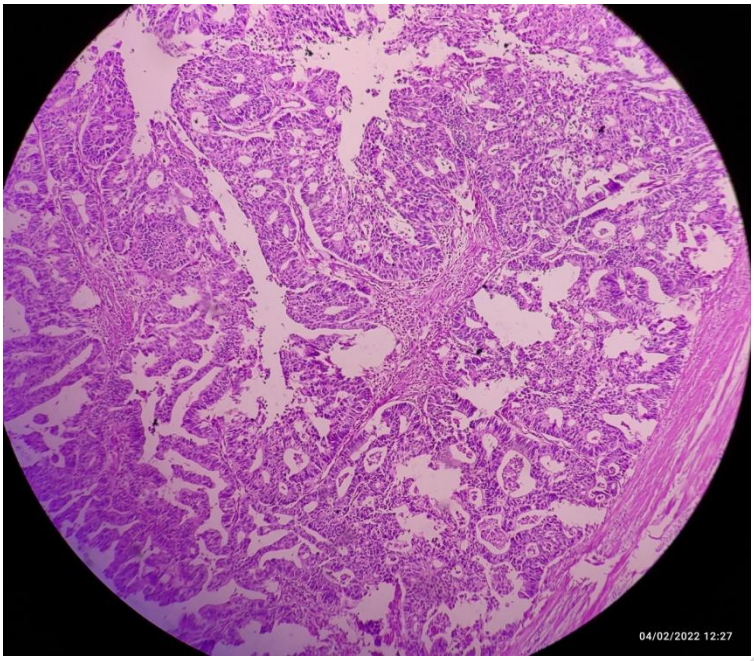

Image2 : H&E (40x) Moderately differentiated periampullary adenocarcinoma

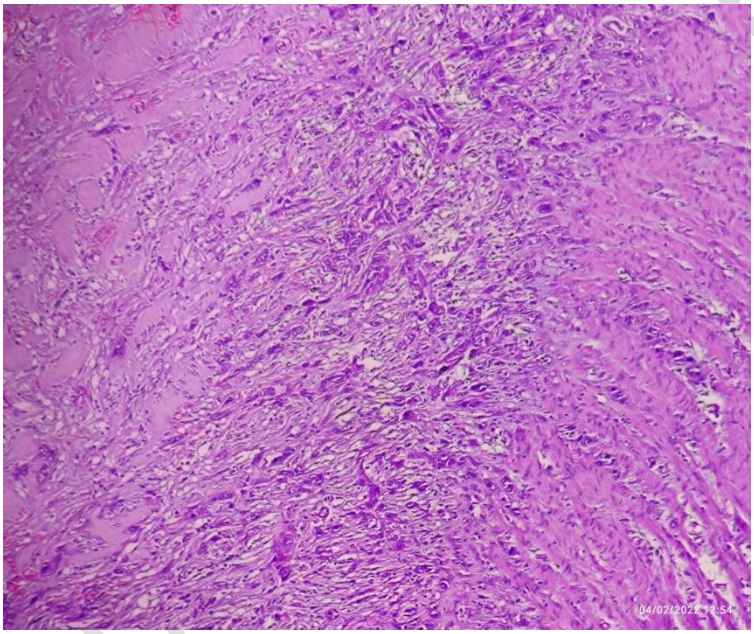

Image3 : H&E (40x) Poorly differentiated periampullary adenocarcinoma

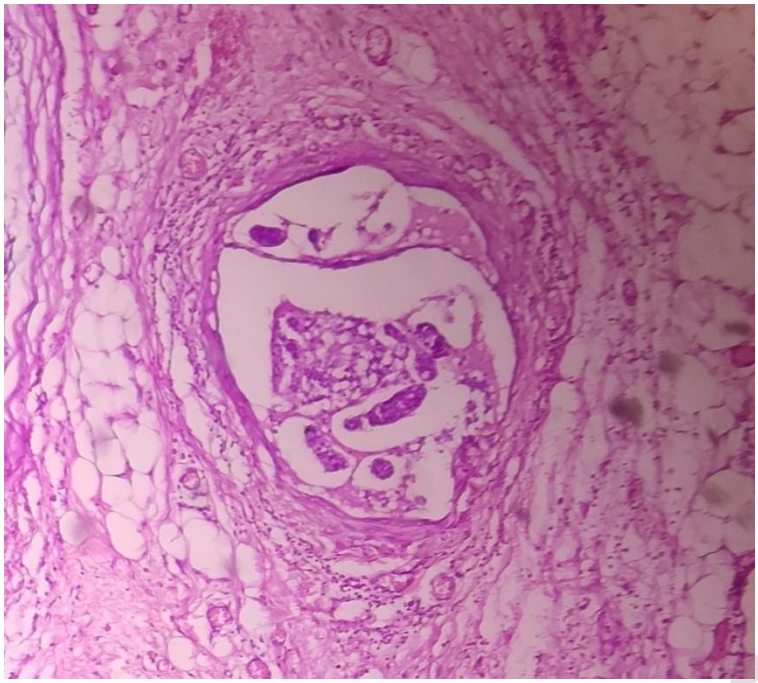

Image4 : H&E (10x) Tumour deposits in a lymphovascular channel

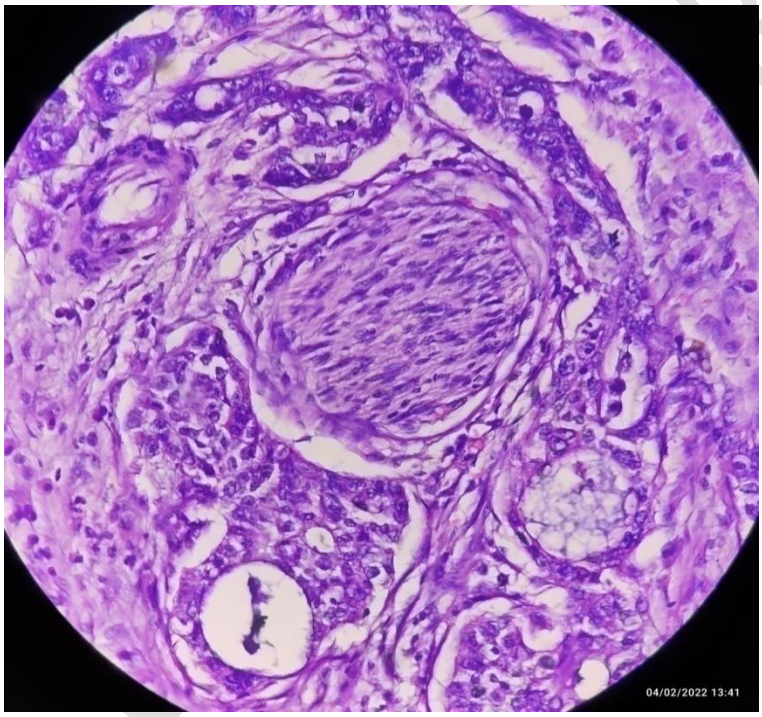

Image5 : H&E (40x) Perineural invasion

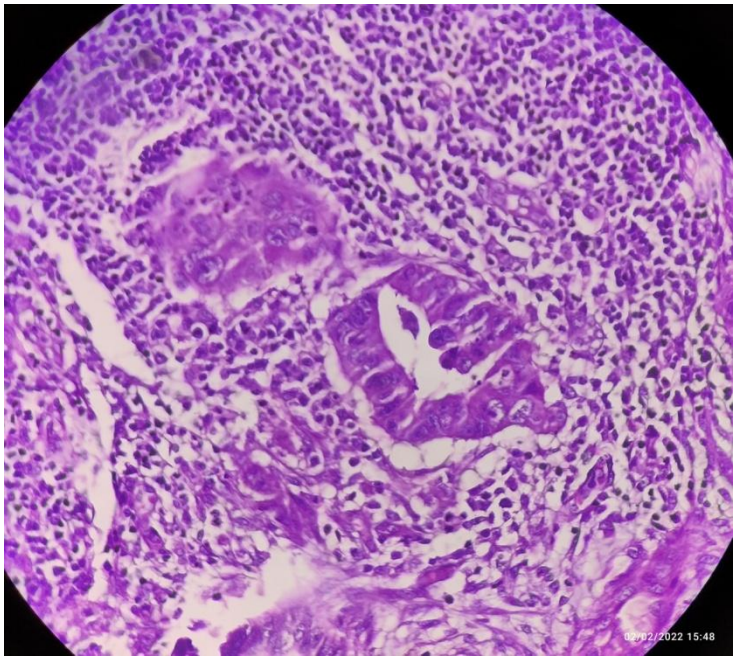

Image6 : H&E (40x) Lymph node showing tumour deposits

Table 4 : Post Operative Complications

Complications	No of Cases	Percentage of Cases
Wound Infection	29	19.3%
Pancreatic leak	28	18.6%
Delayed Gastric Emptying	22	14.6%
Postoperative Haemorrhage	9	6%
Resurgery	6	4%
Bile Leak	3	2%
Postoperative Mortality	6	4%

4. Discussion

Whipple's pancreaticoduodenectomy is performed as a lifesaving procedure for a variety of tumours. The long term survival depends on the pathology of the resected specimens. Surgery is the cornerstone of treatment with chemotherapy playing a supportive role. On estimation, the five year survival rate of cases undergoing Whipple's resection was 10 to 25%.[19]

Ampullary adenocarcinoma constitutes about 0.2% of all the gastrointestinal tumours.[20] In United States periampullary adenocarcinomas accounts for more than 30000 cancer related deaths per year ranking these tumours as the fifth leading cause of cancer deaths in the country.[21] Pancreatic malignancy is the fourth most common fatal malignancy in United States [22] and sixth in Europe.[23]

Ampullary carcinomas have a male predominance and are usually seen in their seventh decade. Age incidence in ampullary carcinomas was stated as 69.7 years by Henson ED et al.[24] Howe JR et al stated the mean age incidence as 65.6 years[25] and Yeo JC et al stated it as 64 years with a male dominance.[26] The mean age incidence in our study was 49.6 years. This is similar to the study results of Din NU et al[27] and Ibrahim SS et al[28] who stated it as 46.7 and 44 years respectively with equal sex incidence. In our study the sex ratio for ampullary carcinomas was 1.6:1 and for ampullary carcinomas was 1.5:1. The overall sex ratio was 1.4:1.

In our study 141 (94%) cases comprised of malignant tumours, 6(4%) showed tumours with low malignant potential and 3 (2%) were of benign nature. Foroughi F et al in their study observed that 13.7% cases had benign lesions.[9] Margijske et al reported 15% lesions as benign in their study.[29] 650 Whipple's specimen analysed by Yeo CJ et al revealed 32% as benign, 5% as neuroendocrine tumours, 4% as pancreatic cystadenoma, 2% as GIST and 67% as malignant lesions.[30]

Periampullary carcinoma was the predominant tumour in our study. This is in synchronization with the findings of Foroughi F et al.[9] However separate studies done by Howe JR et al[25] and Duffy JP et al [31]reported ampullary carcinomas as the predominant entity. Our study revealed ampullary carcinomas as the second most common type. As per Saraee A et al[32] and Landis SH et al[33] pancreatic adenocarcinomas are the commonest findings in Whipple's resection specimens in the Western population. This finding is supported by the studies of Yeo CJ et al[30] who stated this data as 62% and Michelassi F et al[34] as 85%. These differences may be due to variations in geographical demography and study sample size. An extensive study of larger sample size would reveal the pancreatic carcinoma incidence in the Indian sub continent. Moreover not all pancreatic tumours undergo Whipple's pancreaticoduodenectomy resection.

Study done by Howe JR et al stated that among the ampullary carcinomas 66% were of intestinal type and 27% were pancreatobiliary in nature.[25] This is in correlation with our study.

Multivariate analysis of 443 periampullary adenocarcinoma cases done by Yeo JC et al stated that tumour dimension of more than 3cm, nodal metastasis, positive resection margins and a higher tumour grade adversely affected the patient survival.[30] The mean size of ampullary and periampullary tumour in our study was 2.2cm and 2.7cm respectively. Study by Howe JR et al concluded that tumour size more than 2cm, pancreatobiliary type, presence of LVI, PNI, lymph node metastasis and positive margins were associated with decreased survival rates.[25]

76.19% cases of ampullary adenocarcinomas and 71.42% of periampullary adenocarcinomas were moderately differentiated in our study. Similar results were given by Duffy JP et al.[31] On the other hand Foroughi F et al[9] and Dhakwa R et al[35] reported a greater percentage as well differentiated namely 60% and 80% respectively.

55.08% of periampullary and 28.57% of ampullary carcinomas showed the presence of LVI in our study.

Lymph node metastasis contributes to tumour staging and predicting survival outcomes.[36] 64.41% of periampullary and 38.09% of ampullary carcinomas had tumour deposits in lymph nodes in our study. Nodal metastasis was 40% and 52% in separate studies conducted by Warren KW et al[37] and Alema JH et al[38] respectively.

Margin status is an important prognostic marker. We had only one specimen of margin positivity. Study conducted by Yeo JC et al on 201 patients stated the five year survival in margin negative cases as 26% (median survival 18 months) compared to cases with margin positivity 8% (median survival 10 months).[30]

Most patients were diagnosed in locally advanced pathological stage (T2, 66.67%) in our study, followed by late stage (T3, 19.04%) and very few in early stages (T1, 14.29%). This finding highlights that a more precise assessment and clinical evaluation can lead to early cancer detection.

Pancreatic endocrine neoplasms comprise less than 3% of all pancreatic tumours.[24] Their mean age of presentation is 55 to 60 years and are more common in males. Younger age incidence are usually associated with MEN Syndrome and VHL Disease.[39] Majority of these are non functional tumours carrying a grave prognosis. It is an indolent tumour having a comparatively better prognosis than pancreatic adenocarcinomas.[40] We got two cases of pancreatic endocrine tumour, both presenting in females, with an age incidence of less than 50 years. Ibrahim SS et al's study also had similar results.[28]

SPN is a tumour of the young females. Our study reported 4 cases, having a mean age of 18 years with a female predominance. Study by Patil TB et al states the mean age as 20 years.[41] This is a tumour of low malignant potential with localized tumour surgery as treatment of choice.

We also reported single case each of duodenal GIST and mucinous cystic neoplasm of the pancreas. Both these tumours are grouped under low malignant potential tumours.

Whipple's pancreaticoduodenectomy is a complex surgical procedure with high complication rates. None the less, the morbidity and mortality have dramatically reduced owing to the improvement in surgical techniques, intensive care management and post operative care. For most people it takes about two to six months to get back to a normal quality of life.[42] The commonly encountered post operative complication, of wound infection was reported as 7% - 13.3% in various studies done in USA[43,44] while a study done in Germany stated it as 7.2%.[45] Our study observed wound infection rate of 19.3%. These variations are largely related to the intraoperative management, latest surgical modalities and post operative patient care.

Rate of pancreatic leak and post operative haemorrhage was estimated as 18.6% and 6% respectively by us. Karim SAM et al[46] and Saraee et al stated the same as 21.4% and 12.2%, and 7.1% and 7.1% respectively.[47] Saraee A et al further stated delayed gastric emptying rate and bile leak as 32.9% and 2.9%.[47] We noted delayed gastric emptying in 14.6% and bile leak rate of 2%. 5% cases had to undergo resurgery and the perioperative death rate was 4% in a study conducted by Karim SAH et al.[46] Saraee A et al reported 21.4% cases

undergoing resurgery and 37% cases being readmitted for various reasons.[47] Our study stated 4% cases undergoing resurgery and a post operative mortality rate of 4% which is close to <5% rate reported by other centers.[42,48]

Whipple's pancreaticoduodenectomy has been associated with a high rate of morbidity (40% - 60%) and mortality rate of upto 20%.[49] Over the decades, perioperative mortality has been reduced from 25% to 4% - 5%. Some centers that perform a high volume of pancreaticoduodenectomy procedures have even lower mortality rates of 1% - 1.5%.[50,51,52]

5. Conclusion

Our study highlights the fact that the important prognostic factors are tumour grade, tumour stage, presence of LVI, PNI, positive margins and lymph node metastasis. This is well correlated by the significant P value of PNI, LVI and lymph node metastasis in our study. Majority of our cases were diagnosed at a relatively advanced stage. A more precise assessment and clinical evaluation along with practical methods can lead to early detection of cancer and timely intervention can improve the survival rates.

Consent

As per International standard or University standard the written consent of all the patients has been taken and preserved by the author(s).

Ethical Approval

Study was conducted after the approval of the ethical committee of IGIMS, Patna vide Letter No – 138/IEC/IGIMS/2021 dated 25/06/2021.

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