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Original Research Paper

An Analysis of Whipple's Resection in Tertiary Care Centre: Prognostic Parameters Revisited

Medical Science

KEYWORDS :

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ABSTRACT

Introduction*: Whipple's surgery remains the main stay of treatment for ampullary and periampullary tumours. This study was undertaken to study the demographic profile, prognostic parameters (lymphovascular invasion, perineural invasion, lymph node metastasis, resection margin involvement) in intestinal and pancreatobiliary carcinomas. Also, postoperative morbidity and mortality were studied in relation to various types of ampullary and periampullary carcinomas in patients where follow up was available.*

Methods *– This is a retrospective study carried out over a decade in a tertiary care centre. Gross and histologic examination of 155 whipple's specimens received during that tenure were reviewed. Follow up was obtained in 32 cases and evaluated with emphasis on perioperative mortality and morbidity.*

Results*- Ampullary adenocarcinomas were the commonest tumours seen in our study. These were closely followed by distal common bile duct (CBD) and pancreatic tumours. There was a significant male preponderance with Male to female ratio of 1.6:1. Postoperative complications were seen in 21.2% cases with mortality seen in 7.9 % cases.*

Conclusion- *Ampullary adenocarcinomas were commonest. Pancreatic adenocarcinomas showed high proportion of perineural, lymphovascular invasion and nodal metastasis. Tumours of distal CBD were more aggressive than other periampullary tumours.*

Introduction :

Whipple's surgery remains mainstay of treatment for periampullary neoplasms, which include those arising from ampulla, head of pancreas, distal common bile duct (CBD) and duodenum. [1]Periampullary region has a complex anatomy and histology. A thorough gross examination and exhaustive histopathological examination of the resected Whipple's specimen is mandatory to determine the origin of tumour. [2] Perioperative mortality and morbidity rates are different for intestinal and pancreaticobiliary subtypes. Kimura et al in 1994 found that Intestinal subtype has better prognosis than pancreaticobiliary subtype. [3] Site of origin, size, type, grade, differentiation, TNM staging, lymphovascular and perineural invasion, positive resection margins of the tumour and lymph node metastasis are important parameters which determine prognosis in patients with periampullary carcinomas.

This study aims to compare tumours arising from ampulla, head of pancreas, distal CBD and duodenum with respect to demographic profile, clinical features, haematological, biochemical and radiological investigations, gross morphology and histopathological features of the tumour. Clinicopathological correlation has been made to compare biological behaviour, perioperative morbidity and mortality of intestinal and pancreaticobiliary neoplasms with respect to outcome of the surgery.

MATERIALS AND METHODS

This is a retrospective study conducted over a decade in a tertiary care hospital. The study group included 155 patients who had undergone Whipple's operation. Specimen was received in the surgical histopathology section of a tertiary care centre. Detailed grossing was done according to standard protocol. Type of specimen received was noted. Dimensions of stomach along greater and lesser curvature, duodenum, pancreatic head and gall bladder in all three dimensions; length and diameter of CBD were recorded. Presence or absence of stent was noted. Stomach was opened along the greater curvature continuing along the anterior wall of pylorus and outer curvature of duodenum. Exposed ampullary region was inspected for presence of site and size of tumour. Gross morphology of the tumour was noted and specimen was evaluated for invasion .Serial cuts were made in pancreatic head in axial plane, perpendicular to the long axis of the duodenum. Lymph nodes were dissected and inspected for metastasis. Multiple sections (4 sections) were taken from the tumour. Resection margins (proximal and distal resection margin, CBD, pancreatic) were studied .Sections were taken from head, body and neck of gall bladder (if received). All the slides were stained with routine hematoxylin and eosin stain. Slides were reviewed to note the presence or absence of the tumour, site of tumour, histological type and differentiation. Depth of invasion, lymphovascular invasion, perineural infiltration, lymph node status and involvement of resection margins were also noted.

Details of demographic profile, preoperative investigations, intraoperative findings and perioperative outcome of the Whipple's operation were obtained from medical record office. Clinical details of patients taken into consideration were age, sex, presenting complaints, clinical signs, comorbid conditions like hypertension, diabetes mellitus, chronic pancreatitis, etc. Preoperative investigations studied were complete blood count, liver function tests, CA 19-9 levels, ERCP, biopsy, fine needle aspiration cytology (FNAC if done), ultrasound examination and CT scan findings. Perioperative complications and follow up was studied in cases where it was available. Statistical analysis was carried out using Chi Square test.

Results:

There were a total of 155 whipple's resection specimens which were received in surgical histopathology section, out of which 2 cases had no tumour, one case was of benign adenoma of ampulla and one was of type 1 choledochal cyst. These 4 cases were excluded from the study group. Therefore, only 151 cases were taken into consideration. 102 /151 cases (74.17%) were in the age group between 41-70

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years. There were only 9 cases (6%) below 30yrs of age and 12 cases (7.9%) above 70 years of age.

Tumours from ampulla were commonest (101/151) followed by those from CBD and pancreas (22/151) in each and only (6/151) were seen in the duodenum. (Figure1) There were 93 males and 58 females in the study. Males outnumbered the females with a ratio of 1.6:1. Jaundice was the common presenting symptom in 124/151 (82.1%) cases, pain in abdomen was seen in 27/151 cases (17.8%) wherein tumour was located in the pancreas in 16/27 cases (59.25%) cases.

On clinical finding abdominal lump was seen in 26/151 cases (17.2%) out of which 15/26 cases (57.6%) had carcinoma head of pancreas.

CA 19-9 was raised in 96/102 cases (94.1%). Adenocarcinoma 145/151cases (96.02%) was the commonest type of malignant tumour followed by neuroendocrine carcinomas in 03/151 cases (1.9%). (Figure 2) One case each of Mucinous adenocarcinoma, signet ring cell adenocarcinoma and adenocarcinoma with squamous differentiation were seen.116/151 (76.8%) showed moderately differentiated adenocarcinoma followed by well differentiated in 25/151 cases(16.6%)and poorly differentiated in10/151 cases(6.6%). (Table 1) 19/22 cases (86.4%) and 20/22cases (90.9%) of pancreatic cancers showed presence of lymphovascular invasion and perineural invasion respectively .Lymph node metastasis was seen in 17/22 cases (77.3%) and 10/22 cases (45.5%) of pancreatic and CBD carcinomas respectively. Only 9/101 cases (8.9%) of ampullary carcinomas showed lymph node metastasis.(Table 2) Stage 2 tumours were seen in 72 /151 (47.7%) closely followed by stage 1 tumours in 71/151(47%)(Table 3).

32/151 (21.2%) cases showed postoperative complications .Follow up over a period of 30 days was available in 32 patients. 12/32 (37.5%) had expired in the postoperative period. (Figure 3) There was no mortality in the intraoperative period.

Discussion:

Whipple's operation is a routine procedure performed for ampullary and periampullary malignancies. Carcinomas originating from various sites exhibit different clinical behaviour [4] Identification of exact site of origin may be valuable to determine the perioperative morbidity and mortality as every site has its own prognostic factors. This may help surgeons to decide on adjuvant treatment.

In our study, patients' age varied from 31 to 70 years. Maximum numbers of cases were in age group 51 to 60 years with a mean age of 53 years. The youngest patient was a 20 years old male whereas the eldest one was a 82years old male. Yeo et al in their study of 242 patients reported mean age of 64 years.[5] Male preponderance was seen in our study with male to female ratio of 1.6:1. Many studies have reported same sex distribution. Michelassi et al reviewed 647 cases of periampullary tumours and had 63% males in their study[6] 82%cases presented with obstructive jaundice while 18% cases had abdominal pain as chief presenting complaint. Chauhan et al in his study of 24 cases had 100% of cases with jaundice as presenting complaint, other accompanying complaints were pruritus (66.7%), abdominal pain (54.2%), weight loss (54.2%), and vomiting (29%).[7]

Liver function tests showed normal enzyme levels in 11 (7.2%) patients while it was increased in 140 (92.8%) patients. In our study CA 19-9 values was available in only 102 cases out of 151 cases and it was raised in 96 (94.1%) cases. Kim et al in their study of mass screening of 70940 asymptomatic subjects for pancreatic cancers found that number of subjects with a level of CA 19-9 above the cut-off of 37 U/mL was 1063 (1.5%),including four cases diagnosed with pancreatic cancer[8] Ultrasound examination report was available in 134/155 cases and showed periampullary mass with grossly dilated distal common bile duct and pancreatic duct with intrahepatic biliary dilatations in majority of cases. Computed tomography report was available in 137/155 cases which confirmed obstruction by periampullary mass causing abrupt cut off of common bile duct and pancreatic duct. These investigations could not confirm the site of origin of the tumour. ERCP studies carried out in 80/155 cases also showed periampullary mass, preoperative stenting done in selected cases. Biopsy of periampullary mass done in 133 cases showed invasive adenocarcinomas in 124 cases. There were 2 cases of signet ring cell adenocarcinoma while 1 case each of papillary adenocarcinoma, poorly differentiated adenocarcinoma versus neuroendocrine tumour, benign adenomatous lesion and chronic inflammation. Two cases had suspicion of malignancy and 1 case had no tumour on biopsy. The study group of 151 cases was divided into 4 groups according to their site of origin by studying their histological features. The distributions of cancers were seen in ampulla, distal CBD, pancreatic head and duodenum in 66%, 15%, 15%and 4% respectively. Tarazi et al conducted study of 99 patients which showed 46% cases of ampullary carcinomas, 11% cases of distal cholangiocarcinomas, 26% cases of pancreatic carcinomas and 17% cases of duodenal carcinomas.[9]

Histopathology revealed adenocarcinomas in 96.02% cases and 1.9% cases of neuroendocrine tumour. There was one case each of adenocarcinoma with squamous differentiation, ampullary mucinous adenocarcinoma and an ampullary signet ring cell carcinoma. A study conducted by Cameron et al in their study of 145 cases had 63% cases of adenocarcinomas, 3% cases of neuroendocrine tumours and 34% cases of other tumours .[10] The reasons for this could be geographic distribution of different histopathologic types.

The median size of duodenal and ampullary carcinomas were 5.1 cm^2 and 1 cm^2 respectively. Tumours arising from pancreas and CBD had median size of 3.1 cm^2 and 2.2 cm^2 respectively.

Infiltrative growth pattern was most common seen in 53/151 (35%) cases followed by ulcerative pattern was seen in 45/151 (29.8%) cases , nodular growth of tumour was seen in 30 /151 (19.8%) cases, whereas the least common pattern was polypoidal seen in 23 /151 (15.2%) cases. CBD was dilated with a diameter of more than 0.8 cms in 67 /151cases. In study by Abdulkadir et al, CBD diameter was dilated in all 6 cases they studied. [11] 50% of duodenal carcinomas were well differentiated while 76.8%of pancreatic carcinomas and 76.2% of ampullary carcinomas were moderately differentiated adenocarcinomas. Hatzaras et al in their study of 346 periampullary malignancies reported poor differentiation of adenocarcinomas in 34% cases of pancreatic cancers, 25% of ampullary cancers and 28% of cholangiocarcinomas. [12] Perineural invasion is an important prognostic factor associated with poor prognosis. 73/151 cases (48.3%) had perineural invasion. 90.9% , 63.3%, 37.6% and 16.7% cases of pancreatic ,distal CBD ,ampullary and duodenal cancers respectively showed perineural invasion. Hatzaras et al studied 346 pancreaticoduodenectomies and found perineural invasion in 74%,33% and 20% cases of pancreatic cancers, cholangiocarcinoma and ampul-

lary cancers respectively. [12]Chen et al studied survival after pancreaticoduodenectomy in 110 patients and concluded that absence perineural infiltration and lymphovascular invasion was associated with significant improved survival. [13]The present study had 44.3% with lymphovascular invasion. Cho et al suggest that lymphovascular invasion is one of the independent prognostic factor for disease free survival.[14] In our study, lymph node metastasis was seen in 77.3% cases of pancreatic cancer as compared to other sites. Yeo et al reported 72% (106/148) cases of positive lymph nodes were found in pancreatic carcinomas. [5]

5 year survival in pancreatic cancer is 5% as compared to duodenal carcinomas showing survival of 40-50%. [15,16]

Involvement of resection margins was seen in 40.9%, 2%, 13.6%, 16.7% cases of pancreatic, ampullary, CBD and duodenal cancers respectively. Overall 9.9% cases showed R1 resection status i.e. microscopic presence of tumour while 90.1% cases showed R0 resection status i.e. negative for tumour. Raut et al reviewed 360 cases in which he had negative resection margins (R0) in 83.3% and positive (R1) in 16.7 %.[17] Median overall survival was 21.5 months in R1 cases compared to 27.8 months in patients with R0 resection. 47% of our cases were in stage 1 and stage 2 each and 5% cases of stage 3. Foroughi et al reviewed 51 Whipples and found pathologic stage of most of the tumours to be T3 (50.0%); followed by T2 (29.5%), T1 (15.9%) and 4.5% for T4. [18]The postoperative follow up of minimum 30 days was done. 21.2%patients developed complications during the perioperative period with highest cases seen in pancreatic carcinomas (36.4% cases).Overall perioperative mortality in the study was 7.9% accounting for 12 deaths including 6 patients of cholangiocarcinomas and 3 each of pancreatic and ampullary carcinoma. The most common complication was biliary leak in 21.8% followed by wound infection in 15.6%. Other complications observed were pancreatic fistula (12.5%), bronchopneumonia (9.3%), acute respiratory distress syndrome (9.3%), pus in lesser sac (6.2%), anastomotic leak (6.2%), bleeding(6.2%), burst abdomen (3.1%), gastric outlet obstruction (3.1%), septicaemia (3.1%) and acute renal failure (3.1%).Cameron et al reviewed1000 pancreaticoduodenectomies and found mortality rate of 1% with postoperative complication being delayed gastric emptying in 18% cases followed by pancreatic fistula (12%), wound infection (7%), intra-abdominal abscess (6%), biliary leak (2%) and pneumonia (2%), etc. Individual expertise and institutional difference may have contributed to difference in postoperative mortality and morbidity. [19]

Postoperative complications seen in our study included acute respiratory distress in 3 patients, all patients expired, pus in the lesser sac was seen in 2 cases, anastomotic leak was seen in 2 cases, bleeding from operation sites was seen in 2 cases. There was one case each of burst abdomen, septicaemia, gastric outlet obstruction and acute renal failure. 5 patients had comorbid conditions like hypertension, diabetes, coronary artery disease and bronchial asthma. All of them were adenocarcinomas but only two of them showed poor differentiation. Perineural and lymphovascular infiltration were seen in 6 cases, 5 cases had presence of both simultaneously. Lymph node metastasis was observed in 5 cases while R1 resection status was seen in 4cases.Though distal cholangiocarcinoma had maximum perioperative mortality, 66.6% cases of them had comorbid conditions which may be responsible for the poor response of patients to surgical management of the tumour. According to literature distal CBD cancers have less aggressive biological behaviour than pancreatic carcinomas, but our study shows that histomorphological factors like perineural or lymphovascular invasion, nodal metastasis may have impact on immediate postoperative period of these cancers.

Conclusion:

In our study ampullary tumours were common, followed by distal CBD, pancreas and duodenum. The median tumour size observed was 1.44cms. Pancreatic tumours showed a significantly high proportion of perineural, lymphovascular invasion and nodal metastasis. Perioperative mortality was seen in 7.9% cases. Distal CBD were more aggressive than other periampullary tumours.

Table 1: Comparison of histologic grades in periampullary carcinomas

Grade	Tumour Site				Total
	Ampulla	CBD	Pancreas	Duodenum	
WD	18(17.8%)	3(13.6%)	1(4.5%)	3(50%)	25(16.6%)
MD	77(76.2%)	19(86.4%)	18(81.8%)	2(33.3%)	116(76.8%)
PD	6(5.9%)	0	3(13.6%)	1(16.7%)	10(6.6%)
Total	101	22	22	6	151

(WD-well differentiated, MD –moderately differentiated, PD-Poorly differentiated, CBD –common bile duct)

Table 2: Showing comparison between lymphovascular invasion (LVI), perineural invasion(PNI), lymph node metastasis(LN) and resection margin (RM) involvement in different periampullary carcinomas.

	Tumour Site				Total 151 cases
	Ampulla (101 cases)	CBD (22 Cases)	Pancreas (22 cases)	Duodenum (6 cases)	
LVI					
Yes	33(32.7%)	13(59.1%)	19(86.4%)	2(33.3%)	67(44.4%)
No	68(67.3%)	9(40.9%)	3(13.6%)	4(66.7%)	84(55.6%)
PNI					
Yes	38(37.6%)	14(63.6%)	20(90.9%)	1(16.7%)	73(48.3%)
No	63(62.4%)	8(36.4%)	2(9.1%)	5(83.3%)	78(51.7%)
LN metastasis					
Yes	9(8.9%)	10(45.5%)	17(77.3%)	2(33.3%)	38(25.2%)
No	92(91.1%)	12(54.5%)	5(22.7%)	4(66.7%)	113(74.8%)
R M involved					
Yes	2(2%)	3(13.6%)	9(40.9%)	1(16.7%)	15(9.9%)
No	99(98.0%)	19(86.4%)	13(59.1%)	5(83.3%)	136(90.1%)

Table 3: Showing comparison of periampullary carcinoma with TNM staging

TNM	Tumour Site				Total
	Ampulla	CBD	Pancreas	Duodenum	
Stage 1	56(55.4%)	12(54.5%)	1(4.5%)	2(33.3%)	71(47%)
Stage 2	42(41.6%)	9(40.9%)	18(81.8%)	3(50%)	72(47.7%)
Stage 3	3(3%)	1(4.5%)	3(13.6%)	1(16.7%)	8(6.6%)
Total	101	22	22	6	151

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FIGURES (1-4)

Figure 1 – Gross specimen showing ampullary carcinoma.

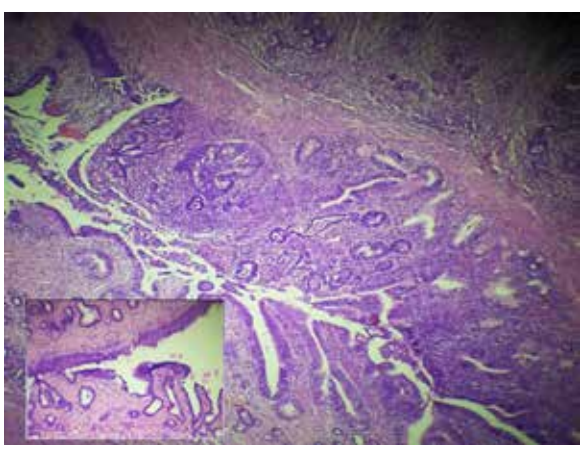

Figure 2- (HE 10X) showing adenocarcinoma of distal Common bile duct (CBD). Inset shows (HE 40X) squamous metaplastic epithelium of distal CBD.

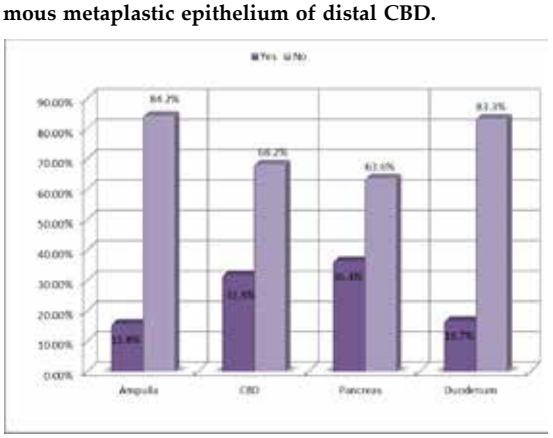

Figure 3-Showing presence or absence of postoperative complications with respect to different sites of periampullary carcinomas (n=151).

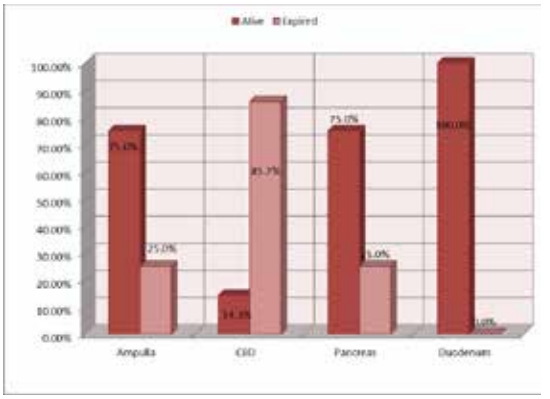

Figure 4-Showing comparison of mortality in presence of complications in cases operated by Whipple's surgery. (n=32)

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