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Research article

PANCREATOBILIARY VERSUS INTESTINAL TYPE OF HISTOLOGICAL DIFFERENTIATION: A COMPARATIVE STUDY WITH HISTOMORPHOLOGICAL PROGNOSTIC FACTORS IN PERIAMPULLARY CARCINOMA

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ABSTRACT

Objectives: Periampullary carcinoma is a term widely used to define a heterogeneous group of neoplasms arising from the head of the pancreas, ampulla of Vater, terminal common bile duct and the duodenum. Periampullary carcinomas typically have either the intestinal type or pancreatobiliary type of the differentiation. The prognostic importance of the type of differentiation is studied in relation to the other prognostic factors like resection margin involvement, tumour size, nodal involvement, vascular infiltration, perineural growth and degree of differentiation. **Methods:** 50 whipples resected specimens were analyzed. In these cases 33 were periampullary carcinomas and the remaining were chronic pancreatitis. The clinical features, laboratory investigations and histopathological features of periampullary carcinomas were studied. Prognostic factors were studied in two histological types of periampullary carcinomas i.e. intestinal type and pancreatobiliary type. **Results:** Out of 33 periampullary carcinomas 24 were intestinal type and 9 were pancreatobiliary type. Periampullary carcinomas were common in females (54.5%) and were seen mostly in the age above 60yrs (36.4%). Jaundice was the most common presenting symptom. Independent adverse prognostic factors seen in the pancreatobiliary type of differentiation were tumor size more than 2.5cm (66.7%), tumor stage, regional lymphnode involvement (77.8 %), vessel involvement (55.6%), perineural growth, areas with poor differentiation (66.7%) and serum CA19-9 levels more than 200U/ml (77.8%). **Conclusion:** In periampullary carcinomas histological type of differentiation is very important independent prognostic factor. In the two histological types of carcinomas pancreatobiliary has worse prognosis when compared to intestinal type.

Key words: Periampullary carcinoma, Pancreatobiliary, Intestinal, Prognostic factor.

INTRODUCTION

Periampullary carcinoma is a term widely used to define a heterogeneous group of neoplasms arising within 1 cm of the ampulla of vater

including head of the pancreas, ampulla of vater, terminal bile duct and the duodenum. Carcinoma originating from these sites exhibit different

clinical behavior.¹ In periampullary adenocarcinoma, the histological and biological features associated with ductal pancreatic adenocarcinoma are different from non-pancreatic Periampullary tumors. The precise origin of Periampullary adenocarcinoma is difficult to determine even with standardized histopathological evaluation particularly if the tumor is large and involves more than one potential site of origin. Adenocarcinoma originating in the ampulla of Vater may be classified as having either “intestinal” or “pancreatobiliary” type of differentiation, of which patients with the latter type consistently have been shown to have worse prognosis.² Tumors of periampullary region were treated by Whipples operation, which involves radical pancreaticoduodenectomy with an extensive gastric resection.³ In our study, we analyzed the different clinicopathological features and prognostic factors in two different histological types i.e. pancreatobiliary and intestinal type of Periampullary carcinomas.

MATERIAL AND METHODS

This study included 50 cases who underwent Whipples pancreaticoduodenectomy for the suspicion of malignancy of the periampullary region. The presenting clinical features and the laboratory investigation findings were recorded. Pancreaticoduodenectomy specimen received in the pathology department was examined after the formalin fixation.

The bile duct and the main pancreatic duct were probed through the ampullary opening in the duodenum and the whole specimen was cut horizontally along the probes. The site of the origin of the tumor is recorded along with the dimensions of the tumor, local tumour extension into the adjacent structures and its relation with the common bile duct and the pancreatic duct. Gross appearance of the tumor is noted (Figure 1). Peripancreatic lymphnodes and the lymphnodes along the common bile duct are examined.

Sections are given from the different areas of tumor, resected end of the pancreatic head, retroperitoneal resection margin, superior part and inferior part of pancreatic head, bile duct resected margin and resected ends of duodenum.

After paraffin embedding all sections obtained were stained by Haematoxylin and Eosin stain. The sections were analyzed to know the histological typing of the tumor and its relation with other prognostic factors like resected margin involvement, vascular invasion, perineural invasion, lymphnode status and serum CA 19-9 levels.

RESULTS

Whipple pancreaticoduodenectomy specimens of 50 patients were studied. Out of which 17 were diagnosed as pancreatitis and 33 were diagnosed as periampullary carcinoma.

The incidence of periampullary carcinomas in both sexes was analyzed and was found to be slightly more in females (54.5%) (Table 1). Incidence in different age groups were also studied by dividing the patients into 5 groups i.e. 20-30 years, 31-40 years, 41-50 years, 51-60 years and above 60 years (Table 2). Maximum numbers of cases were seen in the age group above 60years (36.4%).

The most common presenting symptom in these cases was jaundice (76%). The other symptoms in the order of frequency were anorexia/malaise, weight loss, abdomen pain, steatorrhea, vomiting, fever, malena, back pain and diarrhea (Table 3).

Histologically, the periampullary carcinomas were categorized into intestinal type and pancreatobiliary type. In our study maximum number of cases were of intestinal type (72.7%)(Figure 2,3) when compared to pancreatobiliary type (27.3%) (Table 4) (Figure 4,5).

Different prognostic factors were studied in relation to these two histological types of periampullary carcinomas. Analysis on the tumor staging has shown that maximum numbers of

intestinal type of periampullary carcinoma were in T3 stage and no tumor was in T4 stage. In the tumors of pancreatobiliary type, 2 cases were in T4 stage (Table 5). Association between histological type of differentiation and tumor size were studied by dividing them into two categories i.e. tumor measuring less than 2.5cms and more than 2.5cms. Maximum number of both intestinal and pancreatobiliary type were more than 2.5cms (Table 5). Lymph node involvements in these two histological types of periampullary carcinoma were assessed (Figure 6). Maximum number of intestinal type did not show lymph node involvement whereas in pancreatobiliary type, most of the cases showed lymph node involvement (Table 5). Involvement of deep resected margins in these two histological types of periampullary carcinomas were studied and maximum number of

pancreatobiliary type of periampullary carcinoma showed involvement of deep resected margins (Table 5). Vessel involvement was seen in most of the cases of pancreatobiliary type when compared to intestinal type (Figure 7) and perineural invasion was noted only in few cases of both histological types of periampullary carcinomas (Table 5) (Figure 8). Maximum number of pancreatobiliary type of periampullary carcinomas showed areas of poorly differentiated tumor when compared to intestinal type (Table 5). Serum CA 19-9 levels were analyzed in both the histological types of periampullary carcinomas. Maximum number of pancreatobiliary type of carcinoma had CA 19-9 levels >200U/ml when compared to intestinal type where maximum number of cases had levels <200U/ml (Table 5).

Table.1: Incidence of periampullary carcinoma in different sexes

| Sex | Total (n=33) | Percentages (%) |
|--------|--------------|-----------------|
| Male | 15 | 45.5 |
| Female | 18 | 54.5 |

Table.2: Incidence of periampullary carcinoma in different age groups

| Age group | Total (n=33) | Percentage (%) |
|----------------|--------------|----------------|
| 20-30years | 1 | 3.03 |
| 31-40years | 7 | 21.2 |
| 41-50years | 7 | 21.2 |
| 51-60years | 6 | 18.2 |
| Above 60 years | 12 | 36.4 |

Table.3: Symptoms in periampullary carcinoma

| Symptoms | No. of patients | Percentage (%) |
|-------------------|-----------------|----------------|
| Abdominal pain | 12 | 46 |
| Jaundice | 20 | 76 |
| Anorexia/ malaise | 19 | 73 |
| Weight loss | 19 | 73 |
| Vomittings | 4 | 15 |
| Back pain | 3 | 11 |
| Diarrhea | 2 | 7 |
| Steatorrhea | 12 | 46 |

Table.4: Incidence of different histological types of periampullary carcinoma

| Histological type of differentiation | No of cases (n=33) | Percentage (%) |
|--------------------------------------|--------------------|----------------|
| Intestinal type | 24 | 72.7 |
| Pancreatobiliary type | 9 | 27.3 |

Table.5: Association between the histological type of periampullary carcinomas and various prognostic factors

| Prognostic factors | Intestinal type | Pancreatobiliary type |
|------------------------------------|-----------------|-----------------------|
| Tumor stage | | |
| T1 | 1 (4.2%) | |
| T2 | 11 (45.8%) | 3 (33.3%) |
| T3 | 12 (50%) | 4 (44.5%) |
| T4 | - | 2 (22.2%) |
| Tumor size | | |
| Less than 2.5cms | 9 (37.5%) | 3 (33.3%) |
| More than 2.5cms | 15 (62.5%) | 6 (66.7%) |
| Lymph node status | | |
| No lymph node involvement | 13 (54.2%) | 2 (22.2%) |
| Lymph node involvement | 11 (45.8%) | 7 (77.8%) |
| Resected margin status | | |
| Resected margin not involved | 18 (75%) | 3 (33.3%) |
| Resected margin involved | 6 (25%) | 6 (66.7%) |
| Vessel involvement | | |
| Present | 10 (41.7%) | 5 (55.6%) |
| Absent | 14 (58.3%) | 4 (44.4%) |
| Perineural involvement | | |
| Present | 7 (29.2%) | 1 (11.1%) |
| Absent | 17 (70.8%) | 8 (88.9%) |
| Poorly differentiated areas | | |
| Present | 6 (25%) | 6 (66.7%) |
| Absent | 18 (75%) | 3 (33.3%) |
| CA 19-9 levels | | |
| less than 200U/ml | 20 (83.3%) | 2 (22.2%) |
| more than / equal to 200U/ml | 4 (16.7%) | 7 (77.8%) |

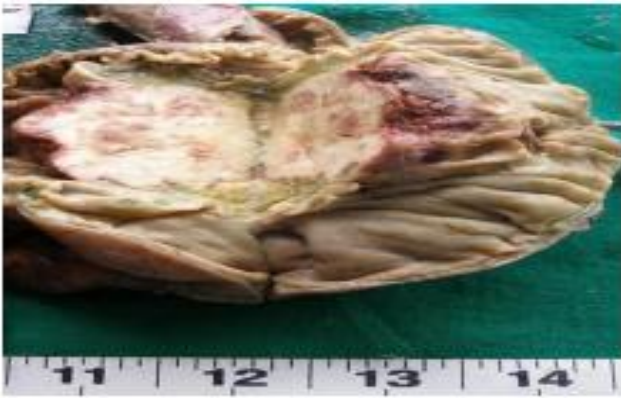


Fig.1: Periapillary carcinoma infiltrating and ulcerating into duodenum

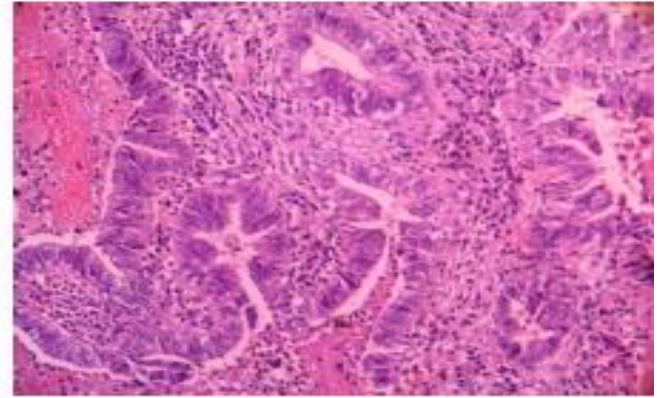


Fig.2: Intestinal type of Periapillary carcinoma with columnar tumor cells (X100)

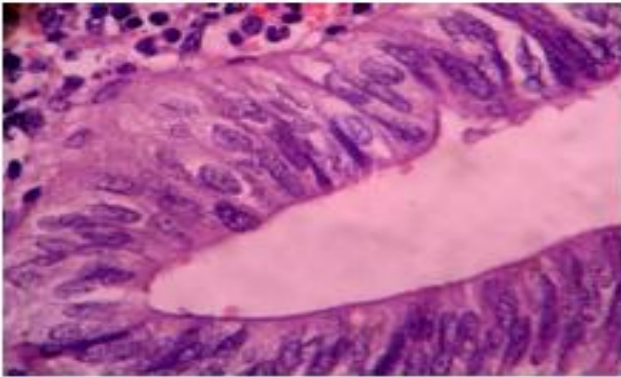


Fig.3: Intestinal type of periapillary carcinoma with columnar tumor cells (X400)

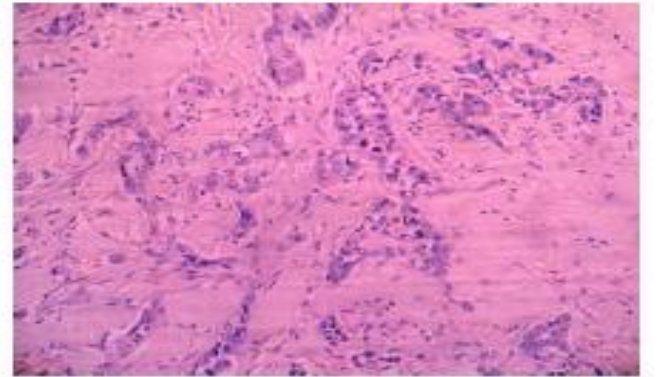


Fig.4: Pancreatobiliary type of periapillary carcinoma with cuboidal tumor cells (X100)

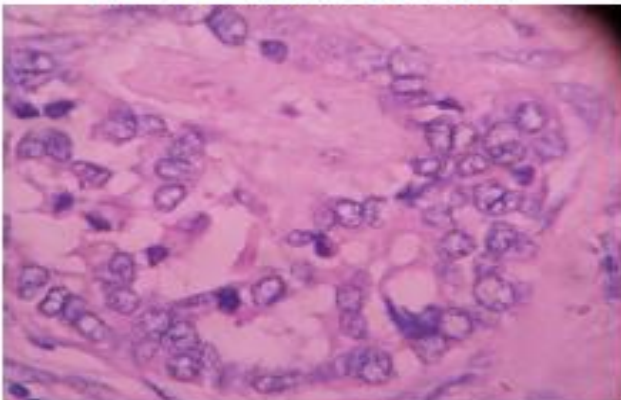


Fig.5: Pancreatobiliary type of periapillary carcinoma with cuboidal tumor cells (X400)

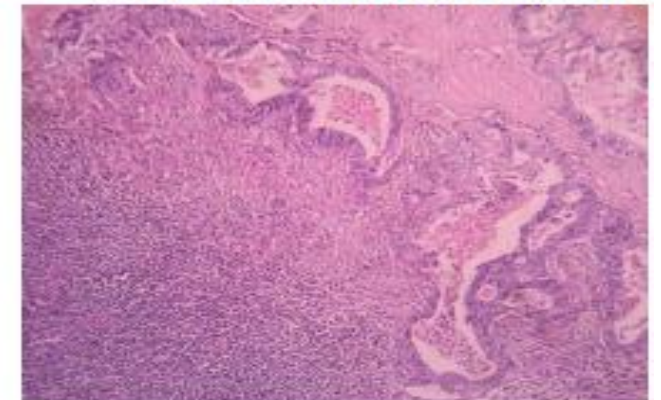


Fig.6: Carcinomatous deposits in lymph node (X100)

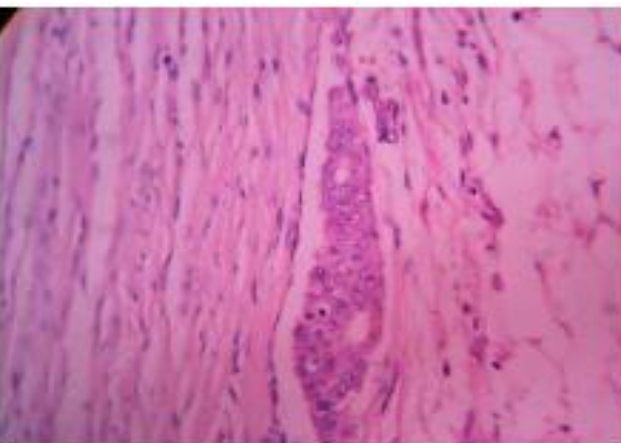


Fig.7: Vascular tumor emboli (X400).

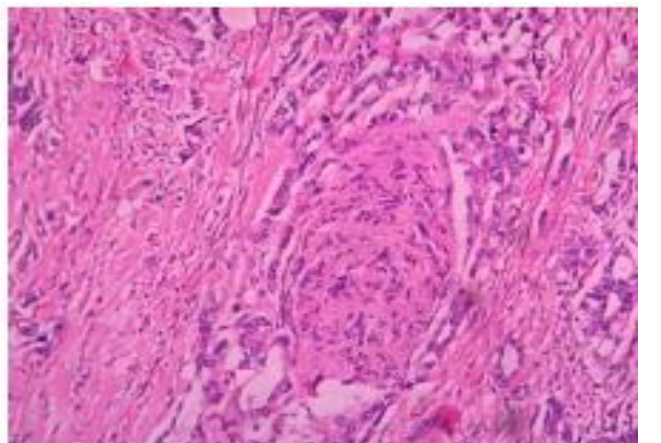


Fig.8: Perineural tumor invasion (X100).

DISCUSSION

Periampullary carcinoma is a term widely used to define a heterogeneous group of neoplasms arising from the head of the pancreas, ampulla of Vater, terminal common bile duct and the duodenum.

In the United States, pancreatic cancer is the 4th frequent cause of cancer death in males as well as females after lung, prostate or breast and colorectal cancer. Each year approximately 30,000 Americans are diagnosed with pancreatic cancer and about the same number die from it. Africans and Americans have appreciably higher rates than whites.⁴ In the studies done by Carlos Chan et al⁵ and in our study the periampullary carcinoma was found to be more common in men. The highest incidence of periampullary carcinoma was found to be in the age group below 60 years in our study and it coincided with the study done by Taxiarchis Botsis et al (2009).⁶ There is increased risk of pancreatic cancer in syndromes like familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC), Peutz-Jeghers syndrome and familial breast ovarian syndrome.⁷ Germline mutations in the few genes including P16 and BRCA2 have been implicated in a small fraction of cases.⁸ Disruption of the PRb, P16INK4 pathways also plays a role in ampullary carcinogenesis.⁹ Other risk factors include chronic pancreatitis, cigarette smoking, increased meat and cholesterol intake and decreased risk with fruits and vegetable consumption.¹⁰

The risk of pancreatic carcinoma is also increased in conditions of excess gastric acidity and by repeated gastrointestinal exposure to N-nitroso compounds or their precursors. The pancreatic ductal epithelium can metabolically activate the carcinogen, if activation has not already occurred in the liver. Chronic secretion, stimulation and N-nitroso compounds exposure potentially overwhelm DNA repair capabilities synergistically to induce tumor development.¹¹

The colonization of *Helicobacter pylori* and history of Diabetes mellitus are also risk factors.

The clinical presentations in patients with periampullary carcinomas are jaundice, abdominal pain, severe and rapid weight loss, nausea and vomiting, pancreatitis and migratory thrombophlebitis. According to Talamini MA et al, in his 28 years experience most common presenting symptom was jaundice (71%) which coincided with our study (76%).¹²

In the periampullary adenocarcinoma it is difficult to identify the site of origin because as the tumor growth invades the adjacent areas and makes it difficult to identify the exact site of origin. In these cases the type of differentiation of tumor either intestinal or pancreatobiliary type is more important prognostically than the anatomic site of origin.¹³

The histological type of differentiation was classified according to the criteria first suggested by Kimura W et al¹⁴ later revised by Albores Savedra J et al.² Pancreatobiliary tumors typically have simple or branching glands and solid nests of cells surrounded by desmoplastic stroma having cuboidal to low columnar epithelium arranged in a single layer without nuclear pseudostratification and the nuclei are rounded. Intestinal tumors typically resemble colon cancer, which consists of solid nests with cribriform areas having tall and often pseudostratified columnar epithelium with oval nuclei, located in the more basal aspects of the cytoplasm and there may also be often presence of mucin. Cases with mixed patterns of differentiation were classified according to the dominant pattern.

Tumor stage and tumor size are the important prognostic factors in periampullary carcinoma. In the studies done by Westgaard A¹³ maximum number of pancreatobiliary types of carcinomas had tumor size more than 2.5cm and were in the stage of T3 which coincided with our study.

Resected margin status is also one of the important prognostic factors which influences the survival of the patients. In the studies done by Westgaard A, maximum number of intestinal type (85%) did not show resected margin involvement and in the pancreatobiliary type of carcinomas, nearly half of the cases showed resected margin involvement.¹³ In our study also maximum number of pancreatobiliary types of carcinomas showed resected margin involvement (66.7%).

The presence of metastatic cancer in lymphnodes excised during pancreatoduodenectomy is generally accepted as an evidence of surgically incurable disease and lymph node dissection is therefore considered to be an important prognostic factor.³ In our study maximum number of pancreatobiliary types of carcinoma showed lymph node involvement (77.8%).

Perineural growth, which is a phenomenon in which cancer cells grow in close apposition to nerves is one of the prognostic factors in periampullary carcinomas.¹⁵ It was suggested that the production of growth factors by the nerves contribute to tumor progression. Over expression of transformed growth factor by the nerves combined with presence of its receptors, epidermal growth factor receptor in the pancreatic cancer cells provides a plausible explanation for the cancer progression by paracrine stimulation.¹⁶ Perineural growth was seen in maximum number of pancreatobiliary type of carcinoma in the studies done by Westgaard A (2008), whereas in our study maximum number of both intestinal and pancreatobiliary type of periampullary carcinomas did not show perineural growth.

Serum CA 19-9 levels above 200U/ml is considered as an independent prognostic factor for patients with resectable pancreatic adenocarcinoma.¹⁷ In our study maximum number of cases with pancreatobiliary type of carcinomas showed CA 19-9 levels more than 200U/ml (77.8%) and most of the cases with

intestinal type of periampullary carcinomas showed less than 200U/ml (83.3%).

CONCLUSION

This diagnostic observational study on 33 patients with periampullary carcinoma gives valuable information about the prognostic importance of histological type of differentiation of periampullary carcinoma. In two histological types of periampullary carcinoma pancreatobiliary type has worse prognosis when compared to intestinal type. The histological type of differentiation acts as an independent prognostic factor in periampullary carcinomas.

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