Original Research Article

A clinicopathological study of histomorphological differentiation and staging of lymph node metastasis in periampullary carcinoma

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ABSTRACT

Background: The periampullary region is an anatomically and histologically complex area that is prone towards malignant transformation. Malignancies in this region have increased in incidence in the last few decades. Classifying these malignancies has become crucial for prognosis and treatment. With the pancreato-biliary type being more aggressive as compared to the intestinal type. Lymph node metastasis and lymph node ratio also aid in prognostication.
Methods: This prospective descriptive study was conducted over one year from August 2022 on 30 patients diagnosed with periampullary tumors who underwent pancreatoduodenectomy and biopsy. Histopathological classification and prognostic factors were analyzed based on Kimura et al classification.
Results: The study included 18 males and 12 females with a mean age of 53.47 years. The origin of the tumor was the head of the pancreas in 66.66% (n=20) of the patients. Adenocarcinoma was the most common histological type. The pancreato-biliary type of adenocarcinoma was more aggressive than the intestinal type when primary tumor size and staging were compared.
Conclusions: Periampullary carcinomas are difficult to classify. Kimura et al classification is an important classification system that helps in the treatment and prognostication of the patient. The pancreato-biliary type of adenocarcinoma is more aggressive as compared to the intestinal type. Lymph node metastasis and lymph node ratio are also important prognostic factors.

Keywords: Histopathological classification, Lymph node metastasis, Periampullary tumors, Prognostic factors

INTRODUCTION

The Periampullary region is a complex area of four histologically and physiologically distinct anatomical structures: the common bile duct (CBD), the head of the pancreas, the ampulla of Vater (AoV), and the second part of the duodenum.[1] It is prone for malignant transformation due to various risk factors.[2-4] Periampullary tumors have increased in incidence in recent years, with them expected to constitute 25% of the Indian cancer burden by 2025.[5-8]

WHO Classification of digestive tumors, 5th edition classifies carcinomas of the ampulla of Vater and attempts to include the periampullary in its classification, they recommend anatomical localization of the tumor of this otherwise small anatomical location.[9,10] Another important classification of periampullary tumors was done by Kimura et al and modified by Albores-Saaveedeera classifying the tumors is necessary as prognosis and treatment depends on the histological subtype, with the pancreato-biliary type being more aggressive as compared to the intestinal type. [11-16] Lymph

node metastasis and lymph node ratio are two independent factors that help in the prognostication of patients.[17-19]

Immunohistochemical studies have been brought forward to classify periampullary tumors. The pancreato-biliary type expresses cytokeratin 7(CK7) and lacks intestinal apomucin MUC2 and is negative for cytokeratin 20(CK20). The intestinal type contains CK20 and apomucin MUC2 and often lacks CK7.[2-4,8,15,20]

Periampullary tumors require further research, with overlapping classifications and opposing schools of thought we attempt to study the validity of traditional classifications. We analyzed 30 patients diagnosed to have periampullary tumors concerning their histopathological classification and prognostic factors.

METHODS

This prospective descriptive study was conducted over one year, in the pathology department of D. Y. Patil Medical College, Hospital and Research Centre, a tertiary-level hospital in Pimpri, Pune from the period of September 2022 to October 2023.

Inclusion criteria

All patients above 18 years diagnosed to have periampullary tumors and undergoing pancreatoduodenectomy (Whipple's procedure) and excision biopsy for histopathological examination were included in the study.

Exclusion criteria

Patients on palliative care were excluded from this study.

The histopathological reporting was standardized as per Kimura et al classification (modified by Albores-Saaveedeera et al).[13] For all the samples included a detailed gross examination was conducted and gross findings were noted, sections for histopathology were given as per 8th edition AJCC guidelines.

Histomorphological features were studied in detail and carcinoma was characterized into intestinal type or pancreaticobiliary based on histopathological examination (HPE). Lymph node samples that were taken were considered positive if the resection section contained a tumor, the lymph node ratio was calculated, and lymph node staging was done as per 8th edition AJCC guidelines.

Statistical analysis

Based on histomorphological classification, the statistical analysis was done on age distribution, male/female ratio, overall tumor size, invasive component size, lymph node metastasis rate, and lymph node metastasis staging.

Categorical variables like sex ratio, lymph node metastasis, and lymph node ratio were expressed as percentages and analyzed using the chi-square test. Quantitative variables like age distribution, size of tumor, and size of the invasive component analyzed using the student t-test. For all the statistical analysis a $p<0.05$ was considered statistically significant.

This study was approved by the ethical committee of the institute. Patients participating in this study gave the informed consent for their participation.

RESULTS

Characteristics of the cohort- demographics of data

The total number of patients in the study was 30, there were 18 males and 12 females the male: female ratio was 1.5, and there was a slight preponderance in males. The youngest patient was 20 years old and the oldest patient was 74 years old, the mean age of all the patients was 53.47 years. The age distribution of the patients is tabulated in Table 1.

Table 1: Age distribution of the patients.

Age group (in years)	Number of patients	Percentage
20-30	2	6.66
30-40	3	10
40-50	5	16.67
50-60	9	30
60-70	6	20
70-80	5	16.67

Pathology of resected specimens

We first classified the 30 specimens anatomically based on the site of origin on the tumor, we found that the origin of the tumor was the head of the pancreas in 66.66% (n=20) patients, ampulla of vater in 20% (n=6), common bile duct in 6.67% (n=2) and duodenum in 6.67% (n=2). We have further classified the tumor according to the histological type encountered, we found that the most common histological type encountered was adenocarcinoma 80% (n=24), followed by pseudopapillary tumor 10% (n=3), neuroendocrine neoplasm 10% (n=3) (Table 2).

Histopathological evaluation and analysis

Thus, the total number of periampullary adenocarcinoma was 24, we classified them according to the Kimura et all classification into pancreato-biliary and intestinal type, and there were 54.16% (n=13) cases of pancreato-biliary adenocarcinoma and 45.84% (n=11) cases of intestinal adenocarcinoma. We studied the age distribution in the two groups and found that the pancreato-biliary type peaked in incidence in the 5th decade of life whereas the

intestinal type peaked in the 6th decade of life, this was statistically analyzed using the student T-test and found no statistical significance between the two groups with a p-value of 0.93. The sex distribution was compared statistically using the chi-squared test and we found no statistical significance between the two groups with a p-value of 0.72. The age and gender distribution is tabulated in Table 3.

Table 2: Anatomical location and histology of the specimen.

	Number of patients	Percentage of patients
Anatomical location		
Head of pancreas	20	66.66
Ampulla of vater	6	20
Common bile duct	2	6.67
Duodenum	2	6.67
Histological type		
Adenocarcinoma	24	80
Pseudopapillary tumor	3	10
Neuroendocrine neoplasm	3	10

Table 3: Comparison of the age and gender distribution between the pancreato-biliary type and the intestinal type.

Distribution (in years)	Pancreato-biliary type		Intestinal type	
	Number of patients	Percentage of patients	Number of patients	Percentage of patients
Age in year				
30-40	1	7.69	1	9.09
40-50	3	23.08	1	9.09
50-60	3	23.08	5	45.46
60-70	4	30.76	2	18.18
70-80	2	15.39	2	18.18
Gender				
Male	8	61.53	6	54.54
Female	5	38.47	5	45.46

Table 4: Comparison of the level of differentiation between the pancreato-biliary type and the intestinal type.

Level of differentiation	Pancreato-biliary type		Intestinal type	
	Number of patients	Percentage of patients	Number of patients	Percentage of patients
Well-differentiated	5	38.46	3	27.27
Moderately- differentiated	3	23.08	6	54.54
Poorly- differentiated	5	38.46	2	18.19

Table 5: Comparison of the primary tumor between the pancreato-biliary type and the intestinal type.

	Pancreato-biliary type		Intestinal type	
	Number of patients	Percentage of patients	Number of patients	Percentage of patients
Stage of primary tumor				
T1	3	53.85	9	81.82
T2	8	61.53	1	9.09
T3	1	7.71	1	9.09
T4	1	7.71	0	0
Lymph node staging				
N0	12	92.31	11	100
N1	1	7.69	0	0
N2	0	0	0	0
TNM staging				
Stage I	2	20.52	8	72.73

	Pancreato-biliary type		Intestinal type	
	Number of patients	Percentage of patients	Number of patients	Percentage of patients
Stage II (A & B)	9	69.22	2	18.18
Stage III (A & B)	1	10.26	1	9.09
Stage IV	0	0	0	0

Another aspect that we analyzed in our study was the level of differentiation, the ratio of well: moderately: poorly differentiated in the pancreato-biliary and intestinal types was 38.46%: 23.08%: 38.46% and 27.27%: 54.54%: 18.19%, the chi-squared test showed no statistical significance between the two with a p-value of 0.267. The results are tabulated in Table 4.

TNM staging

The primary tumor was staged according to the 8th edition AJCC guidelines, and the two subtypes were compared. The staging was compared between the two groups using the chi-squared test and a p-value of 0.013 was obtained, proving a statistically significant difference between the two subtypes. AJCC 8th edition staging was used for the status of lymph node metastasis, the lymph nodes were positive in only 1 pancreato-biliary case. The TNM staging of the tumor was done based on the AJCC classification 8th edition. This study did not have any case of distant metastasis thus the stage was M0 for all the cases. The two types of tumors were statically compared using the chi-squared test and a statistically significant p-value of 0.018 was obtained.

Histopathological prognostic factors

The lymph node ratio was assessed for every patient who had positive lymph node status, the number of lymph nodes assessed were ranging from 5-64, with a mean of 20.5. We classified the lymph node ratio into three categories 0, 0-0.2 and more than 0.2, graphically represented in Figure 1. Due to the paucity of positive lymph node reports, we could not statistically analyze the data.

One of the features of metastasis that we looked for was perineural infiltration, we found that perineural infiltration was present in 92.31% of the pancreato-biliary type and absent in the intestinal type. This was analyzed with the chi-squared test and we found no statistically significant difference between the two with a p=value of 0.477.

Lymphovascular spread is also an important factor in metastasis. But our study did not show significant levels of lymphovascular spread. The graphical representation of lymphovascular spread can be seen in Figure 2.
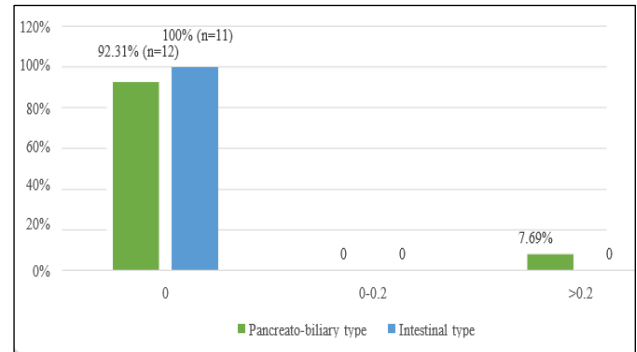

Figure 1: Graphical representation of the comparison of the TNM staging between the pancreato-biliary type and the intestinal type.
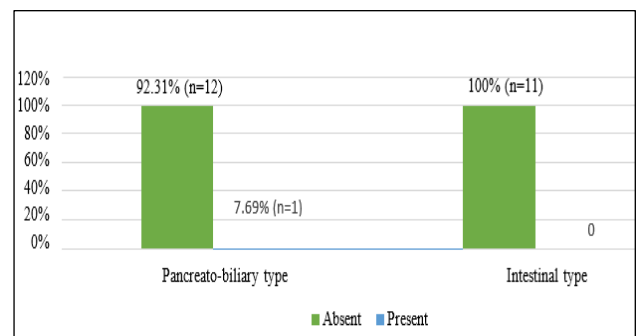

Figure 2: Graphical representation of the lymphovascular spread in the pancreato-biliary type and the intestinal type.
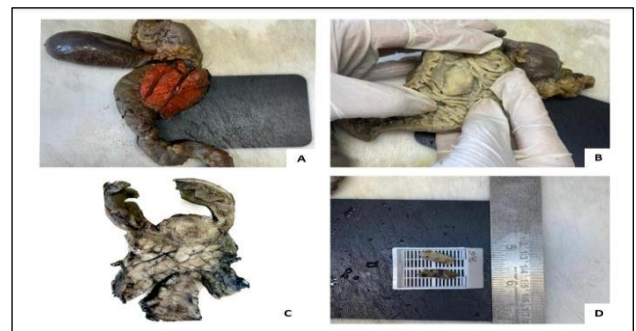

Figure 3: (A) Gross-pancreatoduodectomy speciemen with the cut of of the stomach (Whipple's procedure); (B) growth in the ampullary region; (C) Transverse cut section of specimen; (D) Hemisected metastatic lymph node.
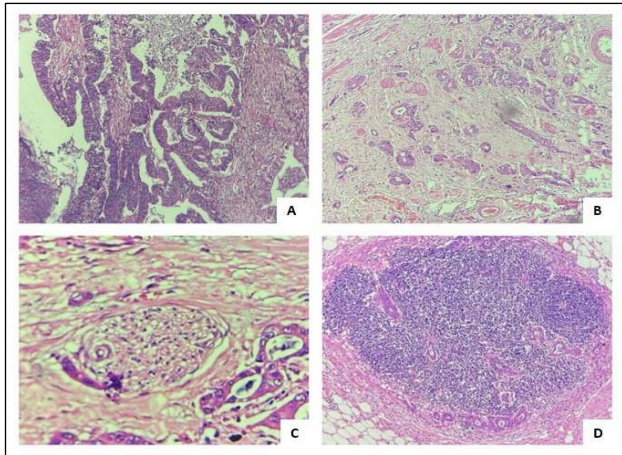
Figure 4: (A) Photomicrograph showing intestinal type adenocarcinoma (200x); (B) Photomicrograph showing pancreato-biliary type adenocarcinoma (200x); (C) Photomicrograph showing perineural invasion by pancreato-biliary type adenocarcinoma (400x); (D) Photomicrograph showing lymph node metastasis by pancreato-biliary type adenocarcinoma (200x).

All the specimens received underwent a gross examination and histopathological examination, we have enclosed the gross photographs and histological photomicrographs as shown in Figure 3 and 4.

DISCUSSION

Periampullary carcinoma presents a challenging case to every surgical pathologist. Over the years this malignancy has increased in incidence with dismal survival rates.[8] Ampullary carcinomas are malignancies with the epicenter being the AoV, WHO recommends further subclassification of this area based on its complex anatomy.[9,10] There have been contrary opinions regarding the prognosis of the patients and treatment protocol.[21] The role of the pathologist is critical here as it has been seen that one of the few important predictors of outcome is the type of periampullary carcinoma. In this study, the prognostic differences between the two types of periampullary carcinoma were evaluated.

There were 30 patients included in the study (18 males, 12 females), the mean age in this study was 53.47 yrs. This was comparable with a study conducted by N. Kumar et al where the mean age was 57.2 yrs.[22] Other similar studies had a higher mean age for patients.[11,18,21,23] Periampullary carcinoma is predominantly present in males this has been validated by multiple similar studies.[11,18,21-23] Anatomically this study showed all 30 patients had periampullary tumors, in the majority of the cases the site of origin was the head of the pancreas, this finding was in general consensus with published literature.[4,15,17,18,24] Wesgard et al in their study found that the pancreatic and periampullary are the most common sites of the tumor.[16] This study classifies the cases histologically with adenocarcinoma being by far the most frequently encountered type 80% [n=24] with rarely occurring histological types like a pseudopapillary, and neuroendocrine.[4,8]

This study classifies periampullary adenocarcinomas based on Kimura et al classification. The pancretico-biliary type was predominant as compared to intestinal type; this is in concordance with previously published articles.[4,8,15,16,18] The intestinal type of periampullary carcinoma was found to occur about a decade earlier than the pancretico- biliary type, but this finding was limited to our study and further studies can be done to evaluate this. This study did not find any statistical difference between the two types based on the level of differentiation.[25,26]

The prognostic difference between the two histological types was one of the primary aims of this study, after classification into pancretico-biliary and intestinal types, the two were compared statically in various aspects.

The tumor was staged according to the AJCC 8th edition guidelines, this study found the pancreato-biliary type has a higher stage of primary tumor as compared to the intestinal type, Wesgard et al in their study found a statistically significant difference between the primary tumor staging and the histological subtype. They also found that intestinal subtype is more often a low-grade tumor, similar results were obtained in various other studies and are corroborated in this study.[16,23] This study could not evaluate lymph node staging and distant metastasis as only one case showed the presence of lymph metastasis.

We could not assess the lymph node ratio as most of our cases did not find positive lymph node metastasis. Bronsert et al in their study found that LNR is an independent predictor of survivability and recommended it in all prognostication algorithms.[4] Saha et al had similar findings in their study. Hurtuk et al in a study found that a positive LNR of greater than 0.2 had worse survival rates than patients with lesser LNR ratios.[19]

In this study perineural infiltration and lymphovascular spread did not demonstrate any statistical significance, this was similar to another study done by Arne Wesgaard on a similar topic. But on reviewing previously published articles, multiple studies report a correlation between the prognosis of the disease and the presence of perineural infiltration and lymphovascular spread, both presenting a negative outcome for the patient.[3,4,18,22,23,27]

This study has few limitations. To confirm the findings of this study analyses of large cohort of patients with periampullary carcinoma is required. Multi centric study can be conducted which will increase the variation in population and will aid is formation of a reliable literature for periampullary carcinoma.

CONCLUSION

This study showed that histological differentiation holds the key to further prognosticating the patient. It forms the basis of immunohistochemistry analysis and molecular typing.

Especially in our country a histological differentiation can be used for prognosticating the patient, this study found that the primary tumor staging and lymph node metastasis and LNR to be significantly higher in pancretico-biliary subtype of periampullary carcinoma, incidicating its poorer prognosis.

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