

**Original Research Article****To Study the Spectrum of Histopathological Variants of Periapillary Carcinoma****Prasuna Chilveri<sup>1</sup>, Bhavani Adepu<sup>2</sup>, Triveni Bhopal<sup>3</sup>**

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**Abstract**

**Introduction:** Periapillary tumours are defined as those that arise within 2 cm of the major papilla in the duodenum. These tumors exhibit different morphology, immunohistochemistry patterns and different clinical behaviors based on the exact site of origin.

**Aim of the study:** To study the spectrum of histopathological variants of periampullary carcinoma.

**Materials and Methods:** This was a retrospective study conducted in Upgraded department of Pathology, Osmania Medical College and General Hospital, Hyderabad over a three year period. A total of 66 cases of periampullary carcinomas resected by Whipples procedure were studied. Histopathologic examination, staging and classification of tumors was done based on site of origin as pancreatic, ampullary, distal common bile duct, and duodenal carcinomas. Immunohistochemistry for CK7, CK20, NSE, Chromogranin A, and Ki67 was done.

**Results:** The maximum number of patients were in the range of 41- 50 years with male: female ratio of 1.6:1. Of the 41 pancreatic periampullary carcinomas, majority were adenocarcinomas (35 cases). Out of 13 ampullary carcinomas 08 were Intestinal type and 04 were Pancreaticobiliary type adenocarcinomas and 01 was neuroendocrine type. Of the 62 periampullary adenocarcinomas, 72.5%, 24.1% and 3.4% were well, moderate and poorly differentiated carcinomas respectively. Pathological TNM staging was done in 62 resected specimens. Majority of the pancreatic adenocarcinomas (24 cases) were Stage III.

**Conclusion:** A combination of tumor size, tumor site, histopathological type and grade, lymphnode involvement and status of resected margins all influence the overall survival of patients undergoing pancreaticoduodenectomy for periampullary carcinomas. Hence, it is important to classify these tumors according to these parameters.

**Keywords:** Periapillary Carcinoma; Anatomical Site; TNM Staging; Histopathologic Variants.

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**Introduction**

Periapillary tumours are defined as those that arise within 2 cm of the major papilla in the duodenum. They

encompass tumours of the ampulla of Vater, the distal common bile duct/CBD (intrapancreatic distal common bile duct), duodenal tumours (usually the second part) involving the papilla and tumours of the pancreatic head involving the ampulla [1,2].

Carcinomas originating from each of these sites exhibit different clinical behaviors [3-6].

Periapillary cancers account for 5% of all gastrointestinal cancers [7,8].

Majority of periapillary carcinomas are composed of adenocarcinomas. The most common periapillary adenocarcinoma is pancreatic adenocarcinoma followed in order by ampillary carcinoma, distal cholangio carcinoma and duodenal adenocarcinoma [9]. While these tumours have different origins, the complex regional anatomy dictates a common operative approach.

Malignant periapillary tumours are best treated by Whipples resection. Surgical removal of periapillary carcinomas remains the only potentially curative therapy [10].

Pathological examination of resected pancreaticoduodenectomy specimens suggests that pancreatic head tumours account for 60%, while tumours of the ampulla of Vater, the Distal CBD and duodenal tumours constitute 20%, 10% and 10% of neoplasms respectively [11].

### **Aim of the Study**

To study the spectrum of histopathological variants of periapillary carcinomas.

### **Objectives**

To study the following parameters in periapillary carcinomas:

1. Anatomical distribution
2. Histopathological types
3. Neuroendocrine differentiation
4. Pathological staging
5. Grading of tumor
6. To predict the prognosis of patients

### **Materials and Methods**

Ethical permission from the institute was taken before starting the study.

The present study was a retrospective study conducted in Upgraded department of pathology, Osmania Medical College and General Hospital, Hyderabad for duration of 3 years from 1st September 2010 to 31st August 2013. Osmania medical college and general hospital is a tertiary referral centre for state of Telangana and also caters to the needs of various districts of neighbouring states.

A total of 66 cases of periapillary carcinomas resected

by Whipples procedure were selected for this study. Clinical data was retrieved from records.

### **Inclusion Criteria**

1. This study includes pancreaticoduodenectomy specimens (Whipples Procedure-Classical or Pylorus preserving) resected for periapillary carcinomas
2. No prior treatment
3. Complete clinicopathologic data (age, gender, histopathological diagnosis, tumor stage, nodal status).

### **Exclusion Criteria**

1. Small biopsies.
2. Non carcinomatous periapillary tumors

The representative tissue bits were fixed in 10% buffered formalin and processed in automatic tissue processor. From the paraffin blocks, 4 to 5 microns thick sections were taken using a microtome. These sections were stained with hematoxylin and eosin.

Histopathologic examination and classification of periapillary carcinomas was done according to the site of origin as pancreatic, ampillary, distal common bile duct, and duodenal carcinomas staging. These cases were further subjected to immunohistochemistry for CK7, CK20, Chromogranin, NSE and Ki 67 to differentiate between intestinal and pancreaticobiliary type adenocarcinomas and to know the proliferation index.

### **Immunohistochemistry**

The kits for CK7, CK20, NSE, Chromogranin, Ki67 immunohistochemical staining were obtained from DAKO Company. Staining was done according to the manufacturer's protocol.

CK 7, CK 20 Positive- Brown cytoplasmic

NSE, Chromogranin A Positive - Brown cytoplasmic

Ki 67 positive- Brown nuclear membrane

### **Observations and Results**

In the present study only resected periapillary carcinoma specimens were studied.

Total 66 cases of periapillary carcinomas were studied. Of the 66 patients with periapillary carcinomas, pylorus preserving pancreaticoduodenectomy was done in 55 cases and classical Whipples procedure was done in 11 cases.

In the present study, the patient age ranged from 21 years to 70 years. The youngest patient was 21 years and the oldest was 70 years. The maximum patients were in

the range of 41 - 50 years and the mean age was 51.47 years.

Of the 66 cases, there were 41 males and 25 females with a male preponderance with a Male:Female ratio of 1.6 : 1.

### **Presentation**

Most common complaints were of jaundice, loss of appetite, pruritus and pain abdomen. All the 66 patients had jaundice.

### **Morphology**

Sizes of the tumors varied from 2 x 2 cm to 4.5 x 4.5 cm. Cut surface of these lesions was grey white, with few showing areas of hemorrhage and necrosis. Serosa was involved in 6 cases. 3 lesions showed presence of glistening mucin grossly. Nodes were isolated in all specimens. Number of lymph node isolated varied from 4-15. The size of lymph nodes varied from 0.5 – 2 cm. Cut section of grossly involved lymph nodes was grey white. The tumor diameter was smallest for ampullary and bile duct cancers (mean 2 and 2.2 cm, respectively) and largest for duodenal cancers (mean 4.0 cm).

Anatomical Distribution of Periapillary Carcinomas according to Site of the four sites of periampillary region, Pancreas, Ampulla, CBD and the Duodenum, majority of periampillary carcinomas were seen in Pancreas 41 (62.1%) followed by Ampulla 13 (19.7%), CBD 7 (10.6%) and Duodenum 5 (7.6%). Of the 66 cases, adenocarcinomas were found in 62 patients (93.9%) and neuroendocrine tumors were found in 4 (6.1%) patients.

### **Microscopy**

Pancreatic periampillary carcinomas: of the 41 pancreatic periampillary carcinomas in the present study, majority (35 cases, 85.3%) were adenocarcinomas.

### **Ampullary Carcinomas**

Out of 13 ampullary carcinomas 08 were Intestinal type and 04 were pancreaticobiliary type adenocarcinomas, 01 was neuroendocrine tumor.

CK7 and CK20 immunohistochemical staining was done to differentiate between intestinal and pancreaticobiliary

type ampullary adenocarcinomas. CK7 was positive in all 04 patients with pancreaticobiliary type adenocarcinomas and CK20 was positive in all intestinal type adenocarcinomas. The neuroendocrine type tumor showed positivity for NSE and Chromogranin.

### **Distal Bile Duct Carcinomas**

Of the 07 bile duct carcinomas 05 (71.4%) were papillary adenocarcinomas and 02 (28.5%) were intestinal adenocarcinomas.

### **Periapillary Duodenal Carcinomas**

There were 5 duodenal carcinomas of which 03 were intestinal type adenocarcinomas, 01 was mucinous adenocarcinoma and 01 was neuroendocrine tumor.

### **Histological Grading**

In the present study, of the 62 periampillary adenocarcinomas, 72.5%, 24.1% and 3.4% were well differentiated, moderately and poorly differentiated respectively. Mucinous adenocarcinomas of intestine by convention are considered poorly differentiated.

### **Lymph Node Metastasis**

There were 33 (53.2%) cases showing lymph nodal metastases and 29 (46.8%) cases did not have any lymph nodal metastases. Nodal metastasis was most commonly seen with pancreatic adenocarcinomas (22 cases) and least common with bile duct tumors (02 cases). None of the tumors showed neural invasion.

### **Resected Margins**

In the present study resected margins were positive in 10 patients (16.1%) and negative in 52 patients (83.9%).

### **TNM Staging**

TNM staging was followed in 62 resected specimens of periampillary adenocarcinomas. Staging of the tumor was done mainly on pathological findings. In all the 62 cases, the distant metastases could not be assessed and were designated as Mx. Majority of the pancreatic adenocarcinomas (24 cases, 38.7%) were stage III.

**Table 1:** Histopathological type of pancreatic carcinomas

Histopathological Type	No. of Cases	Percent (%)
Ductal Adenocarcinomas	35	85.3%
Mucinous noncystic carcinoma	2	5.0%
Adenosquamous carcinoma	1	2.0%
Anaplastic carcinoma	1	2.0%
Neuroendocrine tumors	2	5.0%
Total	41	100%

**Table 2:** Staging of periampullary carcinomas

	Stage I	Stage II	Stage III	Stage IV	Total
Pancreas	13	2	24	-	39
Ampulla	4	8	0	0	12
Duodenum	1	1	2	0	4
CBD	5	2	0	0	7

**Table 3:** Staging and Grading of Neuroendocrine tumors

Age/Gender	HPE Diagnosis and Grade	TNM Staging
33/M	Neuroendocrine tumor, Grade 1	T1N0M0 ( Stage I )
50/M	Neuroendocrine tumor, Grade 2	T3N0M0 ( Stage II )
60/F	Neuroendocrine tumor, Grade 1	T3N0M0 ( Stage IIA )
50/M	Neuroendocrine tumor, Grade 1	T3N0M0 ( Stage IIA )

**Table 4:** Prognostic factors of periampullary carcinomas

	Periapullary adenocarcinomas resected by Whipples procedure			
	Pancreas (n =39 )	Ampulla (n = 12)	Bile Duct (n = 07)	Duodenum (n = 04)
Tumor diameter(cm) (Mean)	3.5	2.0	2.2	4.0
Nodal status (Positive )	24	5	22	2
Nodal status (Negative)	15	7	5	2
Margin status (Positive)	8	2	-	-
Margin status (Negative)	31	10	7	4
Tumor differentiation				
Well	25	10	7	3
Moderate	13	2	-	-
Poor	01	-	-	01

NSE, Chromogranin A, was done in all 66 cases of periampullary carcinomas for neuroendocrine differentiation. Of the 66 periampullary carcinomas, neuroendocrine tumors were found in 4 patients.

A proliferative marker Ki67 was done for these 4 cases and these tumors were graded according to the 2010 WHO grading system for Neuroendocrine tumors. 03 were Grade I Neuroendocrine tumors and 01 was Grade II Neuroendocrine tumor

## Discussion

Periapullary tumours are defined as those that arise within 2 cm of the major papilla in the duodenum. They encompass tumours of the ampulla of Vater, the Distal CBD (intrapaneatic distal common bile duct), duodenal tumours (usually the second part) involving the papilla and the tumours of the pancreatic head involving the ampulla [1,2]. Carcinomas originating from each of these sites exhibit different clinical behaviors [3-6].

Although the modes of presentation and treatment options for these tumors are similar, their prognoses are quite different, with worse prognosis for adenocarcinoma of the head of the pancreas as compared to other periampullary tumors [12]. (The final diagnosis is of great

importance in the outcome of survival analysis after pancreaticoduodenectomy.

Five-year disease-free survival of patients with periampullary tumors will depend on the site and tumor type. Among the patients with periampullary adenocarcinomas, treated by pancreaticoduodenectomy, those with duodenal adenocarcinomas are most likely to survive long term. Five year survival is less likely for patients with ampullary, distal bile duct, and pancreatic primaries, in declining order [13].

Patients with duodenal cancer have the longest survival at five years, ranging from 22% to 53% when compared with other periampullary tumors. Five-year survival is also favorable in patients with ampullary carcinoma, ranging from 34% to 45%. Prognosis will be better for ampullary tumors if neural invasion is absent and if adjuvant chemotherapy is used [14].

Patients with intestinal type of periampullary adenocarcinomas have a significant long survival. Numerous factors have been reported to improve outcome after pancreaticoduodenectomy for pancreatic cancer, including small tumor size, negative lymph nodes, negative resection margins, diploid tumor DNA content, a lesser degree of genetic alteration, and the use of combined-modality chemotherapy and radiation therapy.

For patients with resected ampullary adenocarcinomas, several factors have been variably associated with survival. They include tumor size, histologic differentiation, lymph node status, resection margin status, and perioperative blood transfusion.

For patients with distal bile duct cancers resected by pancreaticoduodenectomy, tumor histology, lymph node status, and resection margin status have been linked to survival.

For patients with duodenal carcinomas, the factor most strongly linked to survival has been lymph node involvement [13]. As observed in the literature, not all studies used similar parameters. Hence, the present study is compared with different studies having similar parameters.

### *The Findings in the Present Study are as follows*

#### *Demographic Profile*

In the present study, the age range was between 21 to 70 years with mean age of 51.47 years and with male predominance (M : F = 1.6 : 1). The mean age in the present study was 51.47 years which is less by 10 years when compared with other studies like that of Cameron et al [15] Yeo et. al. [16] Roest et. al. [17] as seen in the table 5.

#### *Location of Tumor*

The incidence of periampullary carcinomas in the present study was more in pancreas (62.1%) followed by

ampulla (19.7%), distal CBD (10.6%), and duodenum (7.6%). This incidence is similar to most of the studies [16,17], Whereas, the incidence of periampullary carcinomas is more in ampulla (36%) when compared to pancreas (35%) [18,19]. (Table 6).

#### *Tumor Size*

In the present study the tumor size varied from 2 x 2 cm to 4.5 x 4.5 cm.

#### **Histopathological Diagnosis**

In the present study, the commonest periampullary adenocarcinomas were ductal adenocarcinomas of pancreas (35 cases) The present study is similar to that observed by Yeo et. al. [16].

In the present study, of the 12 ampullary carcinomas 08 were intestinal type and 04 were pancreaticobiliary type adenocarcinomas. CK7 was positive in all 04 patients with pancreaticobiliary type adenocarcinomas and CK20 was positive in all intestinal type adenocarcinomas. This incidence in our study is similar to most of the other studies. [20-22] In contrast to our study, Kimura et. al. [23] Zhou et al [24] and Yasunari et al. [25] reported that pancreaticobiliary ampullary carcinoma was the most common subtype than intestinal type adenocarcinomas (Table 7).

In the present study, of the 66 cases of periampullary adenocarcinomas, neuroendocrine tumors were found in 4 (6.1%) patients. Similar incidence was seen in study done by Yeo et. al. [16]. Their study showed

**Table 5:** Incidence of age and gender of periampullary carcinomas – Comparative study

Study	Present study	Cameron et al [15]	Yeo et al [16]	Roest et al [17]
Sample size	66	201	650	121
Mean age (Years)	51.47	65	63	60
Gender ratio, M:F	1.6 : 1	1.6 : 1	1.1 : 1	1.1 : 1

**Table 6:** Location of tumour versus incidence - Comparative study

Location	Present Study	Roest et al [17]	Yeo et al [16]	Michelassi et al [19]	Chan et al [3]
Pancreas	41(62.1%)	51(42%)	282(63.6%)	549(85%)	20(33.3%)
Ampulla	13(19.7%)	30(25%)	70(15.8%)	29(4.5%)	29(48.3%)
Distal CBD	07(10.6%)	21(17%)	65(14.6%)	40(6.0%)	07(11.6%)
Duodenum	05(7.6%)	19(16%)	26(6.0%)	29(4.5%)	04(6.8%)
Total	66	121	443	647	60

**Table 7:** Incidence of ampullary carcinomas - Comparative study

Study	Intestinal type Ampullary Carcinoma (CK20+Ve)	Pancreaticobiliary type ampullary carcinomas (CK7+Ve)	Others (CK7+/CK20+ or CK7-/CK20-)	Total
Present Study	08(66.6%)	04(33.3%)	—	12
Zhou et al [24]	29 (24.2%)	24(20%)	67(55.8%)	120
Romiti et al [21]	11(57.8%)	8(42.2%)	—	19
Yasunari et al [25]	16(37.0%)	18(42.0%)	9(21.0%)	43

5% of neuroendocrine tumors among 650 pancreaticoduodenectomy specimens. 03 Neuroendocrine tumors in our study were of low grade, 01 was of intermediate grade and none were high grade. Similar incidence was seen in a study by Jonathan et al [26].

In contrast to our study some studies showed a higher incidence of high grade neuroendocrine tumors than low grade [27,28].

### Histological Grade

In the present study we observed more of Well-differentiated adenocarcinomas constituting 72.5%

(45 cases), followed by Moderately-differentiated accounting for 24.1% (15 cases) and Poorly differentiated for 3.4% (02 cases).

Mucinous adenocarcinomas of intestine by convention are considered poorly differentiated. In contrast to our study most of the studies in literature had a higher incidence of moderately and poorly differentiated adenocarcinomas than well differentiated adenocarcinomas [16] (Table 8).

### TNM Staging

In the present study, according to the TNM staging 23

**Table 8:** Histological Grade - comparative study

Study	Well differentiated	Moderately differentiated	Poorly differentiated
Present study	72.5% (45 cases)	24.1% (15 cases)	3.4% (02 cases)
Yeo et al [16]	5.25%	67.75%	27%
Chan et al [3]	35%	50%	15%

cases were of Stage I, 13 cases were of stage II, and 26 cases were of stage III. Majority of pancreatic adenocarcinomas were of stage III.

### Conclusion

Periapillary neoplasms excluding those of pancreatic head account for nearly 40% of cases and constitute important subsection that can be treated with optimism compared to more dismal pancreatic head cancers. Pancreaticoduodenectomy (pylorus preserving) offers the best chance of cure.

A combination of tumor size, tumor site, histopathological type and grade, lymph node involvement and status of resected margins all influence the overall survival of patients undergoing pancreaticoduodenectomy for periapillary carcinomas.

Hence, it is important to classify these tumors according to the site of origin, grade and stage of the tumors.

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