

Clinicopathologic Analysis of Periapillary Cancers as Predictors of Survival Outcome: A Hospital Based Study

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ABSTRACT

Introduction: Periapillary carcinomas comprise tumors arising from head of pancreas, ampulla of Vater, distal common bile duct and duodenal papilla. In spite of similar peri-operative outcome, the survival and biological behavior varies greatly in different patients. Hence this study was undertaken to determine the significant predictors of long term survival by analysis of different clinicopathological variables.

Material and Methods: This study was carried out in Department of Pathology and Surgery of S.C.B. Medical College, Cuttack over a period of two years and four months. All cases of periampullary carcinoma subjected to surgery were included in the study. Total 17 clinicopathological parameters were collected in each case and analysed with respect to survival outcome.

Results: There were total 20 cases of periampullary carcinoma included in the study. The overall survival rates at 3 years was 52%. Jaundice, CA 19-9, lymph node metastasis, stage at presentation were found to be independent and better predictors than site of origin.

Conclusion: Analysis of prognosis and duration of survival can be determined by the parameters studied here. Hence all such cases should be subjected to these analytical approach.

Key words: Periapillary Cancers, CA 19-9, Stage, Survival Outcome.

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INTRODUCTION

Periapillary carcinoma arises around the confluence of the common bile duct with the main pancreatic duct. They encompass tumors of the pancreatic head (60% of the resected specimens), ampulla of Vater (20%), distal common bile duct (10%) and duodenal papilla (10%).¹ Thus these tumors are classified on the basis of their tissue of origin. While these tumours can be benign they are most commonly malignant and periampullary adenomas are well known premalignant lesions. Periapillary adenocarcinomas have a better prognosis than adenocarcinomas of the pancreatic head. Incidence of periampullary carcinoma is low, approximately 0.5-2% of all gastrointestinal malignancies and 20% of all tumours of the extrahepatic biliary tree.² The clinical picture of periampullary carcinoma is mainly related in the vast majority of patients to an early occurrence of jaundice, thus contributing to the early detection and a higher resection rate. The macroscopic appearance of periampullary carcinoma includes:

- Intramural tumours: inside the ampulla, without any protrusion inside the duodenum;
- Extramural tumours: Polypoid tumours protruding through the ampullary orifice into the duodenum,

c) Ulcerative cancers of the ampulla, which is associated with worst prognosis.³ While these tumours have different origin the complex regional anatomy dictates a common operative approach. Periapillary adenocarcinomas are best treated by pancreatoduodenectomy (PD). In the majority of higher centres, the surgical morbidity rate still remains as high as 30-40%.⁴ An important observation is that in spite of similar peri-operative outcomes, the long term survival of patients varies greatly. Previous studies attempting to identify significant predictors of survival focus on relatively less risk factors. In order to extend the research in this field, a comprehensive analysis of 17 clinicopathological variables was conducted for identification of predictive factors of survival in patients with periampullary cancer.

MATERIALS AND METHODS

The study was performed on patients with periampullary cancer, who were treated with PD or PPPD at Department of Surgery of S.C.B Medical College and Hospital, Cuttack, Odisha (India) between January 2014 and April 2017. Periapillary cancers including duodenal papilla cancer, bile duct cancer and ampullary

cancer were defined according to WHO classification of tumors [5]. All patients were diagnosed histopathologically by 2 experienced pathologists of the Department of Pathology, SCB Medical College, Cuttack. Operative notes were carefully reviewed to exclude any patient with a tumor arising from duodenum, intrapancreatic distal bile duct, exocrine pancreatic tissue or the endocrine pancreas. All patients provided written informed consent prior to the study.

Seventeen clinicopathological variables (age, sex, preoperative serum total bilirubin, preoperative serum carbohydrate antigen (CA) 19-9 level, operative procedures (PD or pylorus preserving

pancreatoduodenectomy -PPPD), intraoperative blood loss, site of origin of tumor, size of tumor, International Union Against Cancer (UICC) pT factor, lymph node metastasis, UICC stage, histologic differentiation, pancreatic invasion, depth of infiltration, peripancreatic soft tissue invasion, perineural invasion and lymphovascular invasion) were recorded. Tumor was staged in pursuance with the UICC classification⁶⁻⁸, and differentiation grades were defined based on the criteria proposed by Albores-Saavedra et al. The patients were followed up and the 3 year survival rate was calculated. All data was tabulated in the master chart.

Table 1: Clinicopathologic variables in periampullary carcinomas

| SL. NO. | CLINICOPATHOLOGIC VARIABLE | CUT-OFF | NUMBER OF PATIENTS | SURVIVAL RATE IN % |
|---------|-------------------------------------|--|--------------------|--------------------|
| 1 | Age (years) | <50 | 6 | 55 |
| | | ≥50 | 14 | 45 |
| 2 | Sex | Male | 13 | 56 |
| | | Female | 7 | 44 |
| 3 | Total billirubin (mg/dl) | <10 | 15 | 55 |
| | | ≥10 | 5 | 33 |
| 4 | CA 19-9 | <111 | 12 | 58 |
| | | ≥111 | 8 | 38 |
| 5 | Surgical procedure | Pancreatoduodenectomy | 14 | 50 |
| | | Pylorus preserving pancreatoduodenectomy | 6 | 56 |
| 6 | Intraoperative blood loss (ml) | <600 | 15 | 53 |
| | | ≥600 | 5 | 51 |
| 7 | Site of origin | Ampulla | 4 | 58 |
| | | Distal common bile duct | 6 | 36 |
| | | Duodenal papilla | 10 | 57 |
| 8 | Size (cm) | <2 | 6 | 65 |
| | | ≥2 | 14 | 33 |
| 9 | Differentiation | Well | 3 | 65 |
| | | Moderate | 11 | 55 |
| | | Poor | 6 | 42 |
| 10 | Depth | Muscular layer | 4 | 66 |
| | | Overall | 16 | 46 |
| 11 | Pancreatic invasion | Yes | 11 | 38 |
| | | No | 10 | 64 |
| 12 | Peripancreatic soft tissue invasion | Yes | 2 | 26 |
| | | No | 18 | 55 |
| 13 | Perineural invasion | Yes | 3 | 27 |
| | | No | 17 | 54 |
| 14 | Vascular invasion | Yes | 2 | 26 |
| | | No | 18 | 54 |
| 15 | Lymph node metastasis | Yes | 4 | 16 |
| | | No | 16 | 60 |
| 16 | UICC pT factor | I and II | 7 | 72 |
| | | III and IV | 13 | 40 |
| 17 | UICC Stage | I and II | 14 | 60 |
| | | III and IV | 6 | 30 |



Fig 1: Gross photograph of periapillary mass

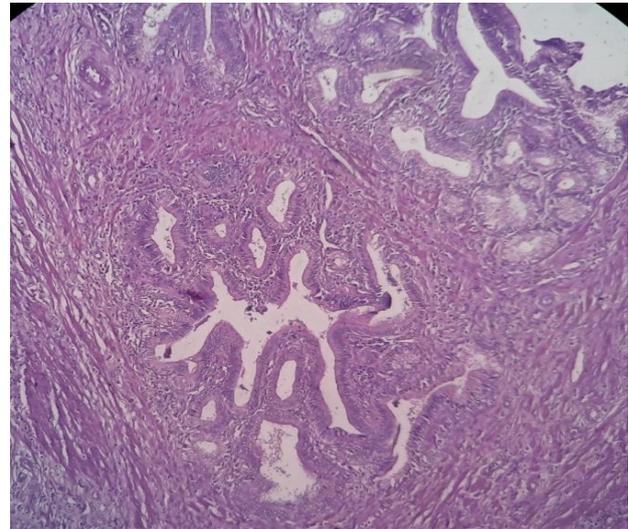


Fig 2: Well differentiated adenocarcinoma (10x)

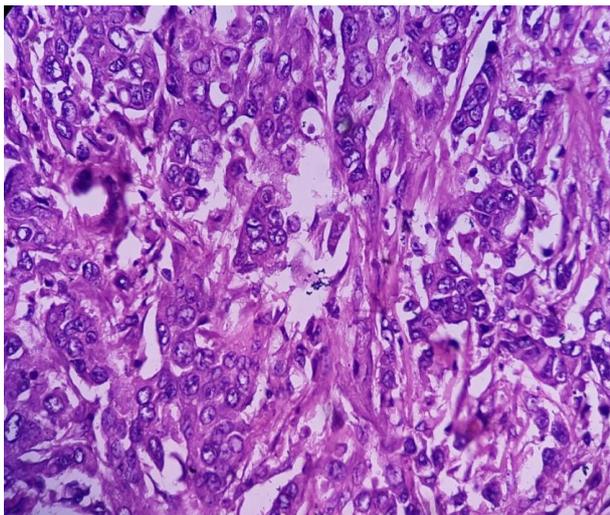


Fig 3: Moderately differentiated adenocarcinoma (40x)

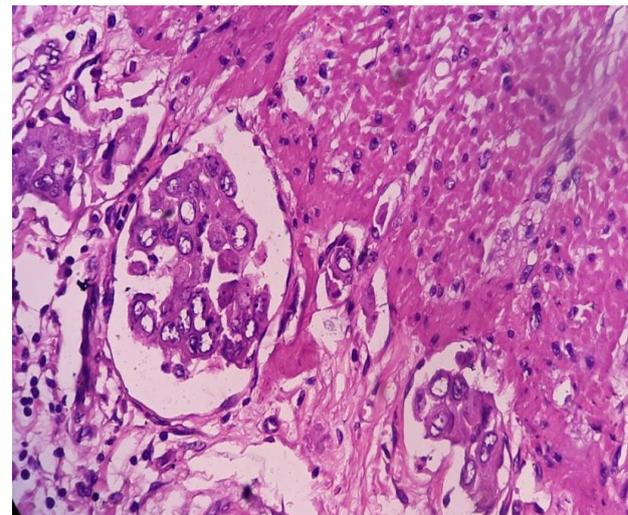


Fig 4: Vascular invasion (40x)

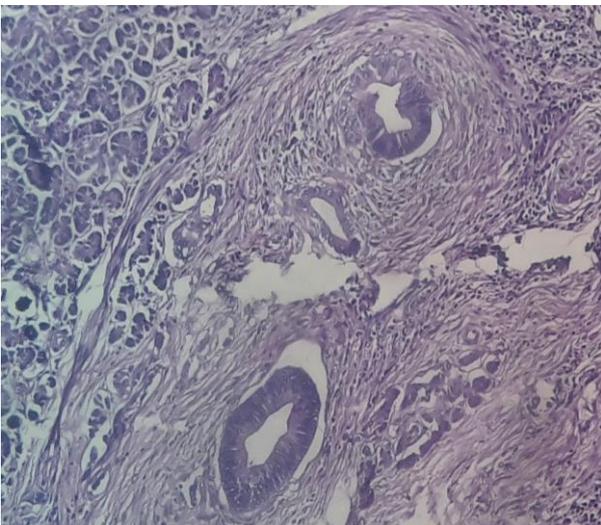


Fig 5: Peripancreatic soft tissue invasion (10x)

RESULTS

Total 20 patients were included in the study. The overall survival rate at 3 years was 52%. Age range was from 32 to 79 with an average of 56 years. 13 were males and 7 were females.(Table 1) 5 patients (25%) presented with serum bilirubin level more than 10 mg/dl and 8 patients (40%) presented with preoperative serum

CA19-9 level more than 111U/ml. PD was performed in 70% patients and 30 % patients were treated with PPPD. 70% patients had tumor size more than 2cm (Fig 1). Site of origin of tumor was identified to be ampulla in 4 patients, duodenal papilla in 10 patients and distal bile duct in 6 patients. Tumor was well differentiated in 3 patients (15%-Fig 2), moderately differentiated (Fig 3) in 11 patients (55%) and poorly differentiated in 6 patients (30%).

11 patients had pancreatic invasion by the tumor and 2 patients showed peripancreatic soft tissue invasion. Perineural invasion was seen in 3 (15%) patients. According to UICC TNM staging, T1 and T2 lesions were found in 7patients (35%) ,T3 in 12 patients and T4 in only one patient. Lymph node metastasis was seen in 20% patients. Additionally 70% patients belonged to stage I-II and 30% to stage III-IV.

Furthermore, ampullary cancers, distant cholangiocarcinoma and duodenal papilla cancers did not significantly differ in CA19-9 level, differentiation degree and lymph node metastasis when they presented at the same stage (Tables 2 and 3). Different types of periapillary cancers at the same stage had similar biologic behavior, indicating that stage may be an important predictor of survival regardless of site of origin. Dudenal papilla cancers had a propensity for lymphovascular (Fig 4), periapillary soft tissue invasion (Fig 5) and perineural invasion.

Table 2: Biologic behavior of different tumor types in the same stages (Stage I and II)

| SL. NO. | VARIABLE | CUT OFF | AMPULLA | DISTANT BILE DUCT | DUODENAL PAPILLA |
|---------|-------------------------|----------|---------|-------------------|------------------|
| 1 | CA 19-9 U/ml | <111 | 1 | 1 | 6 |
| | | ≥111 | 1 | 2 | 3 |
| 2 | Differentiation | Well | 1 | 0 | 2 |
| | | Moderate | 2 | 1 | 4 |
| | | Poor | 1 | 1 | 2 |
| 3 | Lymph node metastasis | Present | 0 | 0 | 2 |
| | | Absent | 2 | 4 | 6 |
| 4 | Lymphovascular invasion | Present | 1 | 0 | 0 |
| | | Absent | 2 | 4 | 6 |
| 5 | Perineural invasion | Present | 1 | 0 | 0 |
| | | Absent | 3 | 4 | 6 |

Table 3: Biologic behavior of different tumor types in the same stages (Stages III and IV)

| SL. NO. | VARIABLE | CUT OFF | AMPULLA | DISTAL BILE DUCT | DUODENAL PAPILLA |
|---------|-------------------------|----------|---------|------------------|------------------|
| 1 | CA 19-9 U/ml | <111 | 1 | 2 | 1 |
| | | ≥111 | 0 | 0 | 2 |
| 2 | Differentiation | Well | 0 | 0 | 0 |
| | | Moderate | 0 | 2 | 2 |
| | | Poor | 0 | 1 | 1 |
| 3 | Lymph node metastasis | Present | 0 | 1 | 1 |
| | | Absent | 0 | 2 | 2 |
| 4 | Lymphovascular invasion | Present | 0 | 0 | 1 |
| | | Absent | 0 | 4 | 1 |
| 5 | Perineural invasion | Present | 0 | 0 | 2 |
| | | Absent | 0 | 3 | 1 |

DISCUSSION

Due to the rarity of periampullary cancers, the paucity of specific papers and the absence of prospective trials no relevant data have been available for the scientific community till the last few years. Quite recently, some articles focused on diagnostic assessment^{9,10} and treatment modalities have been published thus filling a lot of gaps. But the prognostic factors are yet to be explored. Also the long term survival of patients with periampullary cancer varies considerably. So 17 clinicopathological variables were used in the study to identify the significant prognostic factors. The overall survival rate at 3 years was 52%.

Lymph node metastasis has been reported to be an important prognostic factor.¹¹ Gamagami et al. have reported that tumor differentiation is an independent prognostic factor in periampullary neoplasms.¹² In the present study well differentiated cancers had good prognosis than moderately differentiated ones, while poorly differentiated periampullary cancers had the worst prognosis. However according to Hatzaras et al. tumor differentiation is not an independent predictor of survival. The inconsistent results might be due to the relative subjectivity in determining differentiation of tumor. Limited sample size might be another reason.

Serum CA 19-9 has emerged as a valuable biomarker of pancreatic cancer and it has been proved that higher preoperative

serum CA19-9 level predicts poor survival in pancreatic cancer. However there are few studies on the prognostic value of CA19-9 in periampullary cancers. Gao Z et al. have suggested that periampullary cancer patients with preoperative serum CA 19-9 > 35 U/ml are prone to have a poorer survival.¹³ In the present study pre-operative serum level more than 111 U/ml predicted a poorer survival of periampullary cancers (Table -1).

Further noteworthy is the observation that ampullary cancers, distant cholangiocarcinoma and duodenal papilla cancers at the same stage were not different in terms of differentiation grade and lymph node metastasis in this study (Table 2 and 3). It indicates that biologic behavior may be an important predictive factor of survival in periampullary cancers amenable to resection regardless of site of origin. Various studies have compared PD with PPPD and have found no significant difference in survival between them.¹⁴ However published literature has revealed that there is a better postoperative gastrointestinal quality of life in patients who have undergone PPPD in terms of appetite, nausea and diarrhea⁶ and some studies have shown that patients gain better nutritional recovery, weight gain, exocrine function as well as glucose metabolism function when the whole stomach is preserved. In this study patients who had undergone PPPD had better survival outcome than those with PD. Those with III AND IV stage of cancer had poor survival outcome.

Jaundice is an indicator of dismal prognosis in periampullary cancers.^{15,16} This study showed that preoperative total bilirubin level more than 10 mg/dl indicated poor prognosis. It is speculated that jaundice may reflect the bile duct invasion and hepatoduodenal ligament infiltration. In this study lymph node metastasis was found to be associated with poor survival. Additionally in this study the frequency of lymph node metastasis is 18% in patients with ampulla of vater cancers which is much lower than previous reports (38-70%).^{2,7,8} This might be due to the higher rate of duodenal papilla cancer. The study is underpowered by the weakness of limited sample size. Thus better designed studies with more sample size is needed to validate the findings of this study.

CONCLUSION

The authors concluded from the study that prognosis in periampullary cancers is bad in males, in patients with raised bilirubin (>10mg/dl) and raised preoperative CA 19-9 level (>111U/ml), larger tumor size, poorly differentiated ones, with lymph node metastasis and UICC higher stages. PPPD has benefit for survival. So PPPD might be a better choice than PD in periampullary cancers and should be practiced in all institutes for better survival outcome.

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