FACTORS PREDICTING SURVIVAL AFTER PANCREATICODUODENECTOMY FOR PERIAMPULLARY CARCINOMA – A RETROSPECTIVE ANALYSIS

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CERTIFICATE

This is to certify that this dissertation on "**FACTORS PREDICTING SURVIVAL AFTER PANCREATICODUODENECTOMY FOR PERIAMPULLARY CARCINOMA – A RETROSPECTIVE ANALYSIS"** is a bonafide work done by **Dr. S. GOUTHAMAN**, in the Department of Surgical Oncology, College of Oncological Sciences, Cancer Institute (WIA), Chennai under my supervision and guidance, to my satisfaction

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CONTENTS

INTRODUCTION

Carcinoma of periampullary region accounts for 85% of pancreaticoduodenectomies at our institute.Tumours of ampulla of vater are relatively rare, with an crude incidence rate of 0.53 /1,00,000 population per year(1).Overall periampullary cancers account for 5 % of all gastrointestinal tract malignancies(2).A periampullary carcinoma – one arising in the region of ampulla of vater , may be from one of four potential origins- pancreas ,bile duct, the ampulla itself or periampullary duodenum. Surgical series of periampullary tumors have demonstrated that patients with ampullary tumors have a more favourable prognosis than those with pancreatic or bile duct tumors(3,4,5,6,) with median survivals of 30 to 50 months(7,8) and 5-year survival rates between 30% and 50%(9,10).Lymph node metastasis and vascular invasion were found to be independent factors adversely influencing survival in an Indian study(11).Studies attempting to determine important factors affecting survival have been limited by several factors..Most contain small numbers of patients collected over many decades & many do not use multivariate analysis to identify independent prognostic factors.Furthermore , most studies do not assess preoperative factors such as age or biochemical variables.

REVIEW OF LITERATURE

ANATOMY:

Although the ampulla of vater is anatomically a small structure ,it and the surrounding periampullary duodenum give rise to a surprising number & variety of neoplasms that often present with dramatic symptoms because of the strategic location of the ampulla at the confluence of the pancreatic and biliary ducts.The ampulla itself includes several different epithelia : the duodenal mucosa covering the papilla,pancreatic ductal epithelium and that of the distal common bile duct,and the epithelium lining the common channel – the short union of the two ducts within the duodenal wall.The epithelium lining the ducts and the common channel is histologically similar (pancreatobiliary-type epithelium),whereas the papilla is covered by intestinal – type epithelium.

RISK FACTORS

Patients with Familial Adenomatous Polyposis have a markedly higher frequency of ampullary adenocarcinoma ranging from 50 - 86%(12,13) .Histologically proven adenomas of papilla are premalignant & follow the adenoma - carcinoma sequence similar to that seen in the colon(14).

PATHOLOGY:

Periampullary tumours originate from the head of pancreas,ampulla of vater,distal common bile duct and the duodenum.They constitute 30 % of malignant tumours that arise from the pancreatic head region..Periampullary tumours display unique characteristics due to their specific origin.

These tumours are derived either from the epithelium,connective tissue,lymphoid tissue or the neuroendocrine cells.Tumours derived from the epithelium are common as compared to those derived from other parts.WHO has not classified periampullary tumours separately but have included them in the classification of tumours of small intestine.The following is the WHO classification of tumours in the periampullary region.

1. Epithelial tumours
    - Benign – adenoma
    - Premalignant lesions –dysplasia
    - Malignant – adenocarcinoma
2. Neuroendocrine tumours-carcinoids, gangliocytic paraganglioma
3. Stromal tumours – Gastrointestinal Stromal Tumour
    - Lipoma
    - Kaposi s sarcoma
    - Others
4. Malignant lymphomas
5. Secondary tumours

6. Hyperplastic polyps,

- Adenomatous hyperplasia,pancreatic heterotopia.

Carcinoma of the periampullary region:

Periampullary carcinomas are 2 to 3 cm in diameter and are divided into 3 forms;intramural protruding ,exposed protruding and ulcerating form.

CLINICAL FEATURES:

The hallmark clinical presentation for periampullary cancer is jaundice,resulting from obstruction of the intrapancreatic portion of the common bile duct. The obstructive jaundice, fluctuates, when the tumor sloughs off .The jaundice is associated with dark urine,light stool, and pruritis.Nonspecific symptoms such as nausea, anorexia ,weight loss,and fatique are common in many patients with periampullary cancer. . Some may complain of pain in the upper abdomen, emaciation, dark stools, anemia and upper gastrointestinal obstruction. On initial presentation, jaundice is the most common physical finding.Evidence of cutaneous scratching is commonly present,secondary to pruritis.Abdominal examination reveals hepatomegaly with palpable gall bladder.

Pruritus is a well-recognized manifestation among patients with liver diseases and intrahepatic or posthepatic cholestasis. The pruritus is generalized and more intense on hands, feet and around tight-fitting clothes, while face, neck and genital area are rarely involved . The pathogenesis is still poorly understood, as the precise substance responsible for it is not known. Some authors believe it is caused by the

bile acids in the blood (cholemia) or skin , but there is a poor correlation between the skin concentration of bile salts and intensity of pruritus. Recently, an elevation of endogenous opioids was found in the blood of these patients , and treatment with the opiate antagonist naloxone improved pruritus. The itch in patients with cholemic pruritus can be lessened by treatment with cholestyramine, phototherapy, plasmapheresis which lower or remove the unknown circulating pruritogen; antihistamines can be used as adjuvants. Ursodeoxycholic acid has been used (10-15 mg/kg) with good success. Interestingly, some serotonin subtype-3-receptor antagonists like ondansetron, given intravenously, have been helpful in the treatment of cholestatic pruritus.

INVESTIGATIONS:

Laboratory analysis often reveals elevated liver function studies,reflecting the degree of biliary obstruction . In deeply jaundiced patients with malabsorption of fat soluble vitamins ,prolongation of the prothrombin time may be seen.

US, CT and MRCP are widely used because of their availability and non-invasiveness. The role of these techniques in the diagnosis of ampullary carcinoma will continue to evolve with experience accumulated.

ULTRASONOGRAPHY:

Ampullary carcinoma presents two signs on US,(15) direct sign: a lump echo in the ampullary region of the common bile duct, and indirect sign: distention of

intrahepatic and extrahepatic ducts and distention of the duct of Wirsung. These signs are accompanied with gallbladder enlargement, muddy stones, and common duct stones. Although US is noninvasive, intestinal gas and costa influence the images of the tumor at the distal end of the common bile duct and the papillary region. Experienced ultrasound specialists judge the tumor by the images of echo calcification and fibrosis, or on the basis of dilatation of intrahepatic and extrahepatic bile ducts. Clinically, the incidence of common duct stones is higher than that of ampullary carcinoma, so ampullary carcinoma is often misdiagnosed as common duct stone when strong echoes are found to be accompanied with a sound shadow in the common bile duct. Because of the obscure localization of the lesion, it is difficult to distinguish ampullary carcinoma from periampullary carcinoma including carcinoma of the pancreatic head and carcinoma of the lower segment of the common bile duct by US. Thus US should be used as a method for initial screening of ampullary carcinoma.(16)

CT ABDOMEN & PELVIS:

CT is commonly used clinically and has a higher accuracy in detecting diseases of the abdominal cavity. It is difficult to distinguish ampullary carcinoma from periampullary carcinomas such as carcinoma of pancreatic head and cholangiocarcinoma in the lower common bile duct.(17). The diagnosis of ampullary carcinoma by CT is dependent on a soft-tissue mass of Vater's ampulla and the local irregular filling defect of the descending duodenum. The double duct dilatation sign (dilatation of the whole segment of common bile duct, dilatation of pancreatic duct), gallbladder enlargement and dilatation of intrahepatic and extrahepatic bile ducts are

indirect signs of this disease (18, 19). It is highly suspected when CT presents the thickening wall of the descending duodenum and its accretion with the head of the pancreas. Pancreatic cancer characterized by hypovascularity is seen on enhanced CT as a low-density mass in the uncinate process and the head of the pancreas. It grows around the lumen, and infiltrates into the blood vessels, bile duct and pancreatic duct easily. When the pancreatic cancer infiltrates into the pancreatic duct and common bile duct, it causes stenosis and dilatation of the pancreatic duct and the common bile duct. Enhanced CT can effectively detect pancreatic carcinoma with the acquisition of two sets of images after infusion of contrast material. The first phase after infusion takes place during the arterial enhancement. It is useful to detect tumor vascular encasement and the maximum difference of tissue attenuation between normal greater pancreatic enhancement and hypodense pancreatic mass. The peak parenchymal enhancement shown by helical CT may improve the sensitivity of CT in detecting small tumors confined within the pancreas. The second phase takes place during the venous or portal enhancement to provide useful information about venous encasement and hepatic metastasis. Extraglandular extension appears as soft-tissue attenuation thickening obscuring the perivascular fat with deformity, thrombosis or occlusion of the vessels. In cases of venous occlusion, collateral vein and dilatation of small veins around the head of the pancreas can be identified (20).

Cholangiocarcinoma is a malignant tumor arising from the epithelia of the bile duct, and mainly occurs in the hepatic hilum clinically. In early stage, the tumor infiltrates into the wall of the bile duct, leading to irregular stenosis of the lumen. Cholangiocarcinoma in the lower common bile duct is relatively rare, but it is similar

to ampullary carcinoma and differential diagnosis is necessary. Enhanced CT shows the shadow of irregular stenosis in the pancreatic segment of the common bile duct, papillary tubercles which intrude the lumen and the upper common bile duct dilatation without the pancreatic duct dilatation, which are helpful to distinguish between cholangiocarcinoma and ampullary carcinoma.(21,22,23). CT also shows the localization and extension of the carcinoma, and the presence or absence of remote metastasis.(24) Moreover, the thin-section multidetector CT can effectively distinguish ampullary carcinoma from benign papillary stricture(25).

. Conventional ultrasonography is an easy and safe examination, does not entail radiation exposure ,and is relatively inexpensive.Both CT and Ultrasound confirm the obstructive nature of jaundice by demonstrating dilated intrahepatic & extrahepatic biliary radicals.Morrin et al studied 23 patients with periampullary cancer using both multiphase helical CT and ultrasonography with Doppler and found close congruence both in the ability of two studies to predict vascular involvement and in their ability to image metastasis.(26) Currently,multidetector computer tomography with three dimensional reconstruction is the preferred imaging modality to diagnose and stage periampullary & pancreas.(27)

ERCP & MRCP:

MRCP is highly accurate in detecting the obstruction and dilatation of the biliary system. However, it is difficult to reveal the small mass at the ampulla. MRCP can provide intuitive and reliable information about the pancreaticobiliary duct and is

thought to replace diagnostic ERCP.(28). But it fails to provide biopsy and is hard to identify whether the obstruction is benign or malignant. Thus it is used for auxiliary examination before surgical treatment or ERCP.

As a new method for the diagnosis and treatment of diseases of the pancreatic and biliary system, ERCP is highly accurate in detecting malignant biliary obstruction diseases including ampullary carcinoma.ERCP delineates pancreatic duct and common bile duct anatomy.On ERCP, ampullary carcinoma is shown as an irregularly enlarged or cauliflower-like mass, with congestive, erosive and ulcerative surface. On the other hand, the filling defects of benign obstruction such as common duct stones are regular in ERCP (29).

Moreover, ERCP can retrieve biopsy specimens and brush cytology samples for final pathological diagnosis. A biopsy of periampullary mass showing invasive adenocarcinoma will be diagnostic in virtually all cases , however , histologic finding of a benign villous adenoma with or without dysplasia can not reliably rule out malignancy. Some patients may be subjected to interventional therapy including biliary drainage, composite stone dislodgment, biliary tract dilation, and resection of ampullary tumor under ERCP(30).ERCP should be reserved for patients in need for endoscopic stenting,equivocal findings on standard evaluation or for those patients in whom tissue diagnosis is needed.several retrospectivestudies have found fewer complications with the use of preoperative stents.These groups have found no stent related morbidity or an association between stents and woundinfection or wound infection and pancreatic fistula during post operative period for

pancreaticoduodenectomy.Periampullary cancer can be confirmed by several methods preoperatively.

ERCP thus is required to rule out the duodenal papillary lesion when the patient is diagnosed with dilatation of the intrahepatic and extrahepatic bile ducts but without a clear obstruction on US or CT. The detectability of ampullary carcinoma by ERCP is superior to that of US or CT, i.e., a diagnostic accuracy for 95%.(31).

ERCP has its shortcomings. First, its invasiveness produces more complications than other examinations. Second, it cannot detect the infiltration into the surrounding lymph tissue or other organs. Thus it fails to distinguish the stage of the tumor. The ability of Magnetic resonance imaging (MRI) to diagnose and stage periampullary and pancreatic cancer has improved as a result of advances in image resolution acquisition speed ,and Magnetic Resonance cholangiopancreatography (MRCP) (32). Ultrafast spinecho MRI has been reported to be more sensitive than classic CT scanning ,but because of motion artifacts ,lack of bowel opacification,low spacial resolution, and low signal to noise ratio MRI has not been shown to have advantage over modern CT scanning.(33).MRCP holds promise as a noninvasive technique to image the biliary and pancreatic ductal systems in a fashion similar to ERCP.

DIAGNOSTIC LAPOROSCOPY:

Laporoscopy has the potential to detect small surface liver and peritoneal metastasis.When combined with laporoscopic ultrasound ,laporoscopy may allow

evaluation of enlarged lymph nodes,vascular involvement, and deep intrahepatic metastases from periampullary and pancreatic cancer.With the continued improvements in noninvasive imaging modalities, the added value of laporoscopic staging has been questioned.(34).

When ampullary carcinoma is suspected, blood biochemistry tests and US can be done, followed by detection of local extension of the carcinoma by CT, MRCP, or ERCP.

STAGING:

Over the years, multiple systems for staging this tumor have been proposed.

- Martin proposed a 4-stage system, as follows:
  - Stage I - Vegetating tumor limited to the epithelium with no involvement of the sphincter of Oddi
  - Stage II - Tumor localized in the duodenal submucosa without involvement of the duodenal muscularis propria but possible involvement of the sphincter of Oddi
  - Stage III - Tumor of the duodenal muscularis propria
  - Stage IV - Tumor of the periduodenal area or pancreas, with proximal or distal lymph node involvement
- The classification system of Yamaguchi and Enjoji is similar to the Martin classification.
- Talbot et al devised a system that scored tumors according to the degree of infiltration (from 1-4 according to increasing infiltration) and according to tumor

differentiation (from 1-3 for well, moderately, and poorly differentiated tumors), the sum of which separated the patients into 2 groups (scores 2-4 and scores 5-7).

The currently accepted American Joint Committee on Cancer staging system for ampullary carcinoma emphasizes the importance of pancreatic invasion and lymph node metastases. Size has little impact on tumor stage. The definition of primary tumor (T), regional lymph node (N), and remote metastases (M) for classification and staging of cancer of the ampulla of Vater is as follows: (UICC,7th EDITION).

Primary tumor

- TX – Primary tumor cannot be assessed
- T0 – No evidence of primary tumor
- Tis – Carcinoma in situ
- T1 – Tumor limited to ampulla of Vater or sphincter of oddi.
- T2 – Tumor invades duodenal wall
- T3 – Tumor invades pancreas
- T4 – Tumor invades peripancreatic soft tissue or other adjacent organs or structures.

Regional lymph nodes

- NX – Regional lymph nodes cannot be assessed
- N0 – No regional lymph node metastases
- N1 – Lymph node metastases

Distant metastases

- MX – Presence of distant metastases cannot be assessed
- M0 – No distant metastases
- M1 – Distant metastases

Stage grouping of Ampullary Cancers by the TNM System Table:1

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	anyN	M0
Stage IV	anyT	AnyN	M1

PREOPERATIVE BILIARY STENTS:

Table:2

Morbidity Following Pancreaticoduodenectomy: Association with Preoperative Biliary Stents

Group (Reference)	*Stent*	*N*	*Mortality (%)*	*Overall Morbidity (%)*	*Wound Infection (%)*	*P*	*Other Stent-Related Complications*
JHMI (35)	Y	408	1.7	35	10.0	.02	Pancreatic fistula
	N	158	2.5	30	4.0		
Univ. Amsterdam (36)	Y	232	1.2	50	7.3	NS	
	N	58	0.0	55	8.6		
M. D. Anderson (37)	Y	172	0.6	88	13.0	.029	
	N	93	1.0	86	4.0		
University of Bern[a] (38)	Y	50	4.0	56	13.0	NS	
	N	15	0.0	53	10.0		
SGP Institute (39)	Y	54	15.0	48	43.0	.03	Pancreatic fistula
	N	41	10.0	55	24.0		Overall infection
Hines VA (40)	Y	154	2.0	67	8.0	.039	
	N	58	2.0	57	0.0		

JHMI, Johns Hopkins Medical Institutes; SGP: Sanjay Gandhi Postgraduate; VA: Veterans Administration;NS,notsignificant

Biliary stents relieve obstruction and are inserted using percutaneous transhepatic or endoscopic techniques. Soft silastic stents can be changed

periodically, and their use in patients with resectable lesions can maintain a patent CBD during neoadjuvant therapy or referral to a regional center with a focus on pancreatic cancer. Expandable metal stents do not have the interchangeability of silastic stents. These stents are useful for palliation in patients with unresectable tumors. If placed in patients with resectable tumors, the most superior extent of the stent should be at the confluence of the cystic duct and the common bile duct, allowing division of the common bile duct above the cystic duct entrance in any subsequent procedure.

Several retrospective studies have found fewer complications with the use of preoperative stents . These groups found no stent-related morbidity or an association between stents and wound infection or wound infection and pancreatic fistula during the postoperative period for pancreaticoduodenectomy. One of these investigators, Pisters et al.(37) at M.D. Anderson Cancer Center (MDACC) comprehensively scrutinized 300 consecutive patients treated with pancreaticoduodenectomy, finding 172 had been decompressed with a prosthetic stent, 35 with operative bypass, and 93 not drained. Only wound infection was found to be associated with preoperative biliary stenting (stent 13% vs. no stent 4%; P = .029). The bacterial species identified by intraoperative bile culture and at any subsequent wound infection are frequently the same, so the results of an intraoperative bile culture can direct antimicrobial choice when a wound infection is initially suspected.

Preoperative endobiliary stenting is a safe intervention that results in increased rates of postoperative wound infection, but should not be avoided when used to palliate patients for transfer to a high-volume center

OPERATIVE RESECTION:

HISTORY & EVOLUTION OF PANCREATICODUODENECTOMY:

The surgical history of the treatment of periampullary tumors encompasses the past 100 years. Halsted(41) reported the first successful resection of an ampullary tumor in1899, describing a local ampullary resection with associated reanastomosis of the pancreatic and bile duct into the duodenum. Codivilla, near the turn of the century,performed an en bloc resection of the head of the pancreas and duodenum for periampullary carcinoma, but the patient did not survive the postoperative period(42). In 1912,Kausch,(43) a German surgeon from Berlin, performed the first successful pancreaticoduodenectomy in two stages. In 1914, Hirsche(44) reported a successful one-stage pancreaticoduodenectomy. Despite these early attempts at combined pancreaticoduodenal resection in the early part of the 20th century, up until 1935, most ampullary cancers were managed by a transduodenal approach similar to that first performed successfully by Halsted. In 1935, a review by Hunt and Budd(45) described 76 patients with periampullary tumors managed by such an approach, with an operative mortality of 40%.In 1935, Whipple et al.(46) reported three patients with ampullary cancer treated by a two-stage pancreaticoduodenectomy.In 1937, Brunschwig(47) reported extending the indication for pancreaticoduodenectomy to include cancer of the head of the

pancreas. Whipple(46) embarked on perfecting pancreas head resection in 1934, and in the subsequent 30 years he and contemporary surgeons of the period revised the resection to a technique resembling that used by most surgeons today. Early historical procedures utilized a two-stage approach with an initial biliary bypass. Patients demonstrated hepatic dysfunction due to biliary obstruction, and the initial drainage procedure allowed for normalization of coagulopathy prior to a second procedure during which varying amounts of the pancreatic head and duodenum were resected. An evolving understanding of the coagulopathy and the addition of vitamin K to the preoperative regimen of these patients allowed for single-stage procedures to be routinely completed in the 1940s. During the 1940s and 1950s,pancreaticoduodenectomy was accomplished routinely as a one-stage procedure, applied to patients with periampullary neoplasms, and was performed with increased frequency.During the 1960s and 1970s, pancreaticoduodenectomy was a formidable operation, which carried a hospital mortality that approached 25% in some series and led some authors to suggest that its use be abandoned.(48,49) There were, however, exceptions to this high mortality rate, notably a report by Howard(50) in 1968 describing 41consecutive patients treated by pancreaticoduodenectomy without a hospital mortality. In recent years, improved hospital morbidity, mortality, and survival after pancreaticoduodenectomy have been reported.(4,51-53).

In recent years, the indications for pancreaticoduodenectomy have expanded, concomitant with the declining morbidity and improving patient survival. The procedure,whereas applied most commonly with curative intent for periampullary

adenocarcinoma, also can be indicated for a variety of other periampullary neoplasms(8,54-56) . In addition, a recent report has suggested that pancreaticoduodenectomy, when performed with similar perioperative morbidity and mortality rates as can be achieved for palliative bypass procedures, may be associated with improved long-term survival in patients with locally advanced periampullary adenocarcinoma(57).Pancreaticoduodenectomy has been used increasingly in recent years as a safe and appropriate resectional option in selected patients with malignant and benign disorders of the pancreas and periampullary region.The operative mortality rate after pancreaticoduodenectomy is now <4% in many high-volume centers.(4,51,58-60).Although a low mortality rate has been observed,the incidence of postoperative morbidity can approach 50%. Common postoperative complications include delayed gastric emptying, disruption of the pancreatic-enteric anastomosis with subsequent pancreatic fistula, wound infection, and hemorrhage(54,58-60).Many factors may contribute to the declining mortality rate associated with this complex general surgical procedure. There can be no doubt that careful patient preoperative assessment, improved surgical technique,and improvements in perioperative care (including major improvements in interventional radiology and critical care management) all contribute to these declining mortality rates. In addition, recently published data from two large state-wide registries have shown a relation between hospital volume for a complex surgical procedure such as pancreatic resection and perioperative mortality rates.

SURGICAL STEPS:

Evans et al.(61) has described a stepwise methodology that can be applied to pancreaticoduodenectomy and is widely applicable to most resections. This can be summarized as six steps of resection followed by four steps of reconstruction.

Six surgical steps of pancreaticoduodenectomy (clockwise resection).

1. Cattell – Braasch manuevre exposing superior mesenteric vein.
2. Extended Kocher's Maneuvre
3. Portal dissection
4. Transect stomach
5. Transect jejunum and dissect ligament of treitz and rotate jejunum under mesenteric vessels.
6. Transect pancreas and complete retroperitoneal dissection by removing specimen from SMA.

Four steps of reconstruction:

1. End to side pancreatico jejunostomy/Pancreaticogastrostomy.
2. End to side choledochojejunostomy
3. End to side gatro jejunostomy
4. Gastrostomy tubes,jejunostomy tubes,Drains

Intraperitoneal Drains:

Intraperitoneal drains are usually placed intraoperatively in the vicinity of the pancreatic and biliary anastomosis following pancreas resection. A single study prospectively evaluated the contribution of this drainage to the postoperative course. One hundred seventy-nine patients who underwent pancreatic resection (pancreaticoduodenectomy: 139, distal pancreatectomy: 40) were randomized to have drains (88 patients) or no drains (91 patients) placed at the conclusion of the case. Placement of drains did not decrease the need for subsequent percutaneous drainage of an intra-abdominal collection (drain: eight patients, no drain: seven patients) and the incidence of intraperitoneal sepsis, fluid collection, or fistula was increased in the patients who were randomized to intraperitoneal drain (drain: 19 patients, no drain: eight patients)(62). Inexplicably, drains remain widely used in pancreatic resection, and at the least, a duplicate prospective trial is needed from another major specialty center to determine whether this practice should be continued.

Surgical resection of periampullary carcinoma remains the only potentially curative theraphy. Compared with classic pancreaticoduodenal resection(which includes distal gastrectomy), pylorus preserving pancreatico duodenectomy does not seem to be associated with an increase in postoperative complications or other adverse sequelae.(63,64).Equivalent survival and quality of life after both types of resection are available(65,66). Pancreaticogastrostomy is better at least not worse than Pancraticojejunostomy in terms of Complications and Pancreatic leakage.In the

John Hopkins randomized prospective study between 1993-1995, 145 patients were studied.Pancreatic leak rate was 1.7%.No significant difference between PG and PJ. Two small randomized controlled Trials reported a shorter operative time, less blood loss,fewer blood transfusions, and a lower morbidity for PPPD(64,67). However, a larger multicenter randomized controlled trial did not show significant differences between PPPD and SW in all measured outcome(67)..

SURVIVAL:

Five-years survival is favourable in patients with ampullary carcinoma, ranging from 34% to 45%, but recent studies have reported as high as 50%. Factors universally accepted affecting favorably survival were negative resection margins, found in more than 95% of patients, and negative lymph nodes, encountered in 55% of patients. It is controversial whether intraoperative blood transfusion and the degree of tumor differentiation are important.

At the analysis of the survival after pancreatoduodenectomy patients with duodenal cancer have the longest survival at five years, from 22% to 53% when compared with other periampullary tumors. The majority of clinical studies failed to demonstrate prognostic significance for demographic factors or tumor grade. However, resection with negative resection margins found in more than 90% of patients, significantly favoured survival. The influence of positive lymph nodes, occurring in 50% to 65% of patients, on survival is controversial. Several authors

have demonstrated poor prognosis associated with positive nodal status. Conversely, multiple studies have shown that long survival can still be achieved with node positive tumors supporting an aggressive approach regarding resection of these tumors.

The 5 year-survival for patients with distal cholangiocarcinoma is 24%. Factor associated with prolonged survival are negative lymph nodes, found in only 30% of patients and well or moderate tumor differentiation occurring in 60% of resected tumors. Also, it has been noted that 29% of patients with distal cholangiocarcinoma have invasion of extrapancreatic nerve plexus in contrast with only 3% in ampullary carcinoma.

The prognosis of pancreatic adenocarcinoma is one of the most dismal of all cancers, approximately 95% of all patients diagnosed with pancreatic cancer will die within one year. After potentially curative resection the 5 year survival is 5% to 20% making the worst survival of periampullary cancers. Examination of tumor spread reveal a high incidence of nodal involvement (75% of patients) and extrapancreatic plexus invasion found in 60% of patients. After resection, numerous factors have been reported to improve outcome, including tumor size < 2 cm, negative lymph nodes, negative resection margins, diploid tumor DNA content, and a lesser degree of genetic alteration. The influence of combined-modality chemotherapy and radiation therapy is still opened for clinical analysis.

One problem encountered in patients with periampullary cancers after pancreaticoduodenectomy is to confirm the site of origin of these tumors. At the University of Chicago and at the Mayo Clinic, after reviewing their 3-year survivors with presumed ductal carcinoma of the pancreas, investigators found that between 29% and 39% of tumors could not be confirmed to have arisen in the pancreas. Therefore misclassification of tumors is not uncommon and should alert the pathologist that the final diagnosis is of great importance on the outcome of survival analysis after pancreatoduodenectomy.

In conclusion, in ampullary and periampullary tumors resection margin status, resected lymph node status and degree of tumor differentiation significantly influence outcome. Five year survival is most favorable for patients with duodenal cancer, followed in declining order by ampullary tumor, distal bile tumor and pancreatic adenocarcinoma.

Survival after surgical resection is related to the extent of local invasion of the primary lesion, lymph node involvement, vascular invasion, perineural invasion, cellular differentiation, and uninvolved surgical margins. Even a single lymph node with evidence of metastatic carcinoma portends a poor outcome with surgery alone. Exactly which factors are truly independent remains controversial.

PROGNOSTIC FACTORS:

Several retrospective studies have evaluated the factors affecting survival following resection of ampullary carcinomas.Patients with ampullary tumours have a better survival than those with adenocarcinomas of pancreas.(67).However ,reported series are small and often compiled over several decades.Over this period the diagnosis,preoperative staging and treatment of periampullary tumours has evolved significantly.The largest report includes 459 patients from 57 centres in Japan between 1949 and 1974.(68).The largest single institutional series have been reported in the USA (Sloan Kettering ,New York :123 patients,1983-1995(69); John Hopkins ,Baltimore : 120 patients 1969 -1996(8).and Lahey Clinic ,Boston :112 patients (1942-1971)(5).The largest European series are from the Netherands(Amsterdam :67 patients ,1984-1992)(10),France (Rennes:63 patients,1970-1992)(70)Germany (Munich : 66 patients,1970-1992)(71)and the UK (Leicester : 52 patients , 1972-1984)(2).

Nagase et al, from Japan ,studied the experiences with carcinomas of the pancreas, ampulla of Vater, terminal common bile duct, and duodenum found in a series of 3,610 patients collected from 57 major Japanese institutions compiled over a 26 year period till 1977. Carcinomas of the ampulla and the terminal common bile duct and duodenal regions were the most favourable for resection; usually pancreaticoduodenectomy with an overall mortality of 20.8%. As a result of the large number of pancreatectomies performed, there was also a large number of

postoperative complications, the most frequent being leakage at an anastomotic line. Hemorrhage also occurred frequently.The long term survivals following resection for these lesions were poor. The best mean survival time was 22.7 months for carcinoma of the ampulla of Vater. Patients having resections for carcinoma of the head of the pancreas had a mean survival time of 12.3 months. At 5 years there were few survivors and most of them were patients who had undergone resections for carcinoma of the ampulla of Vater.(68).

Howe et al , from MSKCC , analysed patients with adenocarcinoma of the ampulla of Vater to identify clinicopathologic factors that have an impact on patient survival,,Factors significantly correlated with improved survival were resection ($p < 0.01$), and in resected tumors, negative nodes ($p = 0.04$) and margins ($p = 0.02$) independently predicted for improved survival. In periampullary tumors, the highest rates of resection and overall survival (median, 43.6 months) were found in ampullary carcinoma (69)

Talamini et al found , among patients with periampullary adenocarcinoma ,treated by pancreaticoduodenectomy, those with duodenal adenocarcinoma 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. Resection margin status, resected lymph node status,and degree of tumor differentiation also significantly influence long-term outcome. Particularly for patients with pancreatic adenocarcinoma, 5-year survival is not equated with cure, because many patients die of recurrent disease >5 years after resection.(8) Operative blood transfusions

conferred a poorer 5-year survival rate on univariate analysis but not on multivariate analysis.

Allema et al, from Netherlands found that ,the overall 5-year survival was 50%. Survival was significantly influenced by the involvement of resection margins. After resection with involved margins 5-year survival was 15% and 60% after resection with free margins ($p < 0.001$). Tumor size, lymph node involvement, and differentiation grade had limited and not significant influence on survival. (9)

el-Ghazzawy et al reviewed experiences in the US Department of Veterans Affairs hospitals from 1987-1991, during which time 123 patients were diagnosed with ampullary cancer. In the group that underwent surgical resection, perineural invasion, microlymphatic invasion, vascular invasion, or tumor differentiation did not independently influence survival when the tumors were controlled for stage (72)

Yamaguchi et al compared 18 variables among 8 long-term survivors and 12 short-term survivors with ampullary cancer and found that only perineural invasion and histologic grade were significant.(73)

Akwari et al noted that factors associated with favourable survival were histological differentiation (Broders grade 1,2),absence of nodal metastasis and papillary histologic chracteristics(74).

Recent reviews of single-institution surgical experiences of ampullary cancer have focused on the identification of histopathologic features associated with prognosis and survival. Retrospective review, small patient numbers, and long periods of enrollment limit what can be learned from these studies. However, common themes emerge from these published clinicopathologic analyses.

Lowe et al, from U.S., found , on log rank testing, > or = T3 (24 vs 65 mos, P < 0.01), N1 (25 vs 61 mos, P < 0.01), poor differentiation (24 vs 44 mos, P = 0.01), pancreaticobiliary subtype (23 vs 44 mos, P = 0.01), and PNI (23 vs 44 mos, P < 0.01) were significant for worse survival. By multivariate analysis, N1 disease (hazard ratio [HR] 4.50, 95% confidence interval [CI] 1.16-17.40) and PNI (HR 4.62, CI 1.11-19.21) maintained associations with worse survival, whereas histological subtype did not. N1 disease and presence of PNI demonstrated independent associations with worse survival. Given high percentage of mixed histology, PNI may be more informative than the subtype in predicting outcome for patients with AmpCA.(75)

In a recent review of 450 cases of surgical resection of ampullary adenoma or adenocarcinoma at Johns Hopkins, Winter et al, found that 96.7% of the patients had undergone pancreaticoduodenectomy rather than local excision. These researchers concluded that pancreaticoduodenectomy should be the preferred approach for most ampullary neoplasms that require surgical resection, given that nearly 30% of the JohnsHopkins patients with T1 disease had lymph node metastases. Factors associated with the presence of lymph node metastasis included tumor size $\geq$1 cm

(odds ratio [OR] 2.1), poor histologic grade (OR 4.8), perineural invasion (OR 3.0), microscopic vessel invasion (OR 6.6), and depth of invasion > pT1 (OR 4.3; all $P < 0.05$). Specifically, risk of lymph node metastasis increased with T stage (T1, 28.0%; T2, 50.9%; T3, 71.7%; T4, 77.3%; $P< 0.001$)(76)..

In a retrospective review of 46 consecutive cases of ampullary carcinoma, multivariate analysis by Su et al, showed perineural invasion to be a significant independent predictor of poor prognosis ($P = 0.024$). On univariate analysis, other significant predictors of poor prognosis were T3 and T4 tumors (i.e., pancreatic parenchymal invasion) ($P < 0.001$) and lymph node metastasis ($P = 0.01$)(77).

Uchida et al found that patients with preoperative jaundice had poorer survival than those without jaundice (5-year survival 57.2% vs. 100%, $P < 0.01$)(78).

Bettschart et al ,from U.K.,analysed ,over an 11-year period, 561 patients treated for periampullary tumours, 88 of whom had a histologically proven ampullary neoplasm. Prospectively gathered data were analysed to assess predictors of survival. On univariate analysis, age less than 70 years ($P = 0·015$) and a bilirubin level of 75 µmol/l or less ($P = 0·012$) favoured long-term survival. Among 70 patients who underwent cancer resection, factors associated with significantly worse long-term survival on univariate analysis included poorly differentiated tumour ($P < 0·001$), positive nodes ($P < 0·001$), perineural invasion ($P = 0·001$) and invasion of the pancreas ($P = 0·018$). Multivariate analysis identified positive nodes and bilirubin concentration as independent predictors of survival.(79)

Chan et al,in a retrospective study,analysed the outcome and potential prognostic factors of 60 patients with surgically resected periampullary tumors According to the Cox analysis ,ampullary tumours ,absence of neural invasion and use of adjuvant chemotherapy were significant factors for longer survival of patients with ampullary tumours.(6)

Qiao et al,in a study from China, found that the factors that significantly influenced survival were lymph node status ($P < 0.001$), depth of tumor infiltration ($P = 0.029$), and TNM stage ($P < 0.001$) on univariate analysis. On multivariate analysis, both depth of infiltration and lymph node status were the independent determinants of survival after resection ($P = 0.003$, $P = 0.005$, respectively (80).

Berberat et al , from Germany, found that five-year survival was 50.5%, 29.9% and 24.5% for AmpCA, CholCA and DuoCA, respectively. Multivariate analysis identified low bilirubin levels(<100 micromol/l), R0 resections and absence of surgical complications to be strong independent predictors of survival ($p<0.05$). In AmpCA low tumor stages are also an independent predictor of long-term survival ($p<0.01$). For T1/T2 AmpCA the 5-year survival rate was 61%, whereas none of the patients with a T3/T4 tumor survived 5 years(81).

Yeo et al in a single-institution experience retrospectively reviewed the outcomes in a group of patients treated 5 or more years ago by pancreaticoduodenectomy for periampullary adenocarcinoma survivors. The tumor-specific 5-year actual survival rates were pancreatic 15%, ampullary 39%, distal bile

duct 27%, and duodenal 59%. When compared with patients who did not survive 5 years, the 5-year survivors had a significantly higher percentage of well-differentiated tumors (14% vs. 4%; $p = 0.02$) and higher incidences of negative resection margins (98% vs. 73%, $p < 0.0001$) and negative nodal status (62% vs. 31%, $p < 0.0001$). The tumor-specific 10-year actuarial survival rates were pancreatic 5%, ampullary 25%, distal bile duct 21%, and duodenal 59%. They concluded that among patients with periampullary adenocarcinoma treated by pancreaticoduodenectomy, those with duodenal adenocarcinoma 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. Resection margin status, resected lymph node status, and degree of tumor differentiation also significantly influence long-term outcome. (82)

Jarufe et al from UK,analysed the post-operative outcome, and determining risk factors for survival after pancreaticoduodenectomy for periampullary and pancreatic head carcinoma. : Median actuarial survival for carcinoma of the pancreatic head, ampulla and distal bile duct were 13.4, 35.5 and 16 months, respectively; $p < 0.0001$. On univariate analysis for the whole series, the age < or =60, tumour of the head of the pancreas, lymph node positive, resection margin R1, poorly differentiated tumours, and portal vein invasion significantly decreased survival. On multivariate analysis, poor tumour differentiation, surgical margin, lymph node metastases, and age independently influenced survival. Mortality and morbidity were 4.8 and 29.9%, respectively. (83).

Yokoyama et al , evaluated the correlation between jaundice at initial presentation and the degree of tumor spread and to determine the prognostic significance of jaundice in patients with ampullary carcinoma. Fifty-nine patients who had undergone curative resection for ampullary carcinoma were analyzed retrospectively. Jaundice was defined as a total bilirubin serum concentration of > or = 3 mg/dl. The survival of patients with jaundice (median survival 48 months; cumulative 10-year survival rate 39%) was worse than for patients without jaundice (median survival time not available; cumulative 10-year survival rate 86%) ($p = 0.0014$)(84).

Sommerville et al examined the survival differences between ampullary and pancreatic head carcinomas after pancreaticoduodenectomy.in a retrospective review of patients with ampullary or pancreatic head adenocarcinoma undergoing curative resection during a 6-year period prior to 2000. Histologically, pancreatic cancer was worse, with more lymph node involvement and more positive resection margins and vascular and perineural invasions than found in ampullary carcinoma. The median disease-free and overall survival rates were significantly better for ampullary cancer when compared with pancreatic cancer (17 vs. 9 months [$P = 0.001$] and 35 vs. 24 months [$P = 0.006$], respectively). The actuarial 5-year disease-free and overall survival rates were 4.4% and 10.5%, respectively, for pancreatic carcinoma and 27.9% and 31.8%, respectively, for ampullary carcinoma. Multivariate analysis showed that microscopic resection margin involvement ($P = 0.02$) and involvement of over three nodes ($P < 0.001$) were significant factors affecting the overall survival for pancreatic and ampullary carcinomas, respectively. (85).

Sakata et al, compared the prognostic power of the anatomic location of positive nodes with that of the number of positive nodes. Univariate analysis revealed that both the location ($p<0.0001$) and the number ($p<0.0001$) of positive nodes were significant prognostic factors. Multivariate analysis revealed that the number of positive nodes was an independent prognostic factor ($p=0.007$), while the location failed to remain as an independent variable. The median survival time was 59 months with a 5-year survival rate of 48% in patients with 1-3 positive nodes, whereas all patients with >or=4 positive nodes died of the disease within 29 months of resection ($p=0.0001$). (86).

Brown et al,found that the overall 5-year disease-specific survival was 58% for patients with resectable periampullary carcinomas. Five-year survival was 78% (21/27) in node-negative patients, 73% (25/34) for T1/T2 patients, and 76% (17/23) for well-differentiated tumors compared with 25% for node-positive, 8% for T3/T4, and 36% for poorly or moderately differentiated tumors ($P<.01$). On multivariate analysis, only node-negative disease maintained significance (hazard ratio, 5.2; 95% confidence interval, 1.2-21.9). In all groups, there were no deaths due to disease after 3 years of survival was reached. Pancreaticoduodenectomy is curative in 80% of patients with node-negative ampullary carcinomas. (87).

Schmidt et al,in a retrospective review of a prospectively collected databaseof a total of 516 consecutive patients who underwent PD,analysed patient outcomes and survival factors. Three-year survival was 15% after resection for pancreatic cancer, 42% for duodenal cancer, 53% for ampullary cancer, and 62% for bile duct cancer. Univariate predictors of long-term survival in patients with

periampullary adenocarcinoma included elevated glucose levels, liver function test results, abnormal tumor markers, blood loss, transfusion requirement, type of operation, and pathologic findings (periampullary adenocarcinoma type, differentiation, and margin and node status). Multivariate predictors were serum total bilirubin level, blood loss, operation type, diagnosis, and lymph node status. PD can be performed safely. Long-term survival in patients with periampullary adenocarcinoma can be predicted by preoperative laboratory values, intraoperative factors, and pathologic findings(88).

Van Geenan et al, from The Netherlands, analysed the independent prognostic factors and survival after standard pancreaticoduodenectomy for periampullary carcinomas . In the univariate analysis vein resection, blood transfusion of more than four packed red cells, the presence of tumour positive resection margins, lymph-node metastases and poor tumour differentiation significantly decreased survival. In the multivariate analysis positive resection margins, lymph-node metastases, and poor tumour differentiation independently influenced survival.(89).

Monson et al ,found that patient survival was significantly impaired by microscopic lymphatic invasion, regional nodal metastasis, tumor grade, and the epithelium of origin. In a multivariate analysis, only microscopic lymphatic invasion significantly reduced patient survival. Radical resection for ampullary cancer can be performed with a low morbidity and mortality and should remain the procedure of choice for ampullary carcinoma.(90).

Sudo et al,found that , overall 5-year survival rate was 64% in patients undergoing pancreaticoduodenectomy with lymphadenectomy for periampullary carcinoma . Univariate analysis revealed that T3 and T4 tumor (i.e., pancreatic parenchymal invasion) ($P < 0.001$), lymph node metastasis ($P = 0.01$), and perineural invasion ($P < 0.001$) were significant predictors of poor prognosis. Furthermore, perineural invasion was found to be a significant independent predictor of poor prognosis by multivariate analysis ($P = 0.024$). Pancreaticoduodenectomy with lymphadenectomy for ampullary carcinoma is a safe surgical procedure with an acceptable cure rate. The presence of perineural invasion may be useful for predicting poor prognosis in patients with ampullary carcinoma who undergo potentially curative resection(78).

AIMS & OBJECTIVES

1. To analyse factors influencing survival in a series of patients with periampullary tumours who underwent pancreaticoduodenectomy in a single tertiary referral unit .

2. To examine the results of resection & its impact on clinical outcomes on various typesof carcinomas including Ampullary carcinoma,distal Cholangiocarcinoma & Duodenal Carcinoma.

MATERIALS AND METHODS

Pooled data from patients undergoing pancreaticoduodenectomy for periampullary carcinoma over a 13 year period from 1995 to 2008 was retrospectively evaluated and analysed.

Included in this study were 69 consecutive cases of nonpancreatic periampullary carcinomas ,which during final histological examination proved to be ampullary,cholangial or duodenal origin.All patients had adenocarcinoma of periampullary region.All patients underwent evaluation and treatment at our institute between 1995 to 2008 .

Patients with benign pathologies,neuroendocrine tumours and carcinoma of head of pancreas who underwent pancreaticoduodenectomy were excluded from this study .

All patients underwent thorough clinical examination.Routine hemogram,renal function test, liver function test, chest x ray, electrocardiogram were done for all patients. USG Abdomen & pelvis ,CT abdomen & pelvis were done as part of staging evaluation. ERCP and stenting were done in selected patients either done outside or at our institute.

Patients deemed suitable for resection underwent either a standard pancreaticoduodenectomy or pylorus preserving pancreaticoduodenectomy. Reconstruction was performed with either pancreaticojejunostomy in earlier cases and later on pancreaticogastrostomy, choledochojejunostomy and gastrojejunostomy.

Surgical morbidity included wound infection,biliary leak,pancreatic leak,re-laporotomy and delayed gastric emptying.Pathological assessment included primary tumour site,tumour size,histological type,grade ,margin status,nodal involvement, pericapsular spread and Lymphovascular invasion.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software.Variables influencing overall and disease free survival rates were compared using the Kaplan – Meier method using log- rank comparision(102)..Multivariate analysis was performed with the cox proportional hazards model,entering variables significant on univariate analysis; the results are reported as Odds Ratio with 95 % confidence intervals(103).$P<0.05$ was considered significant.

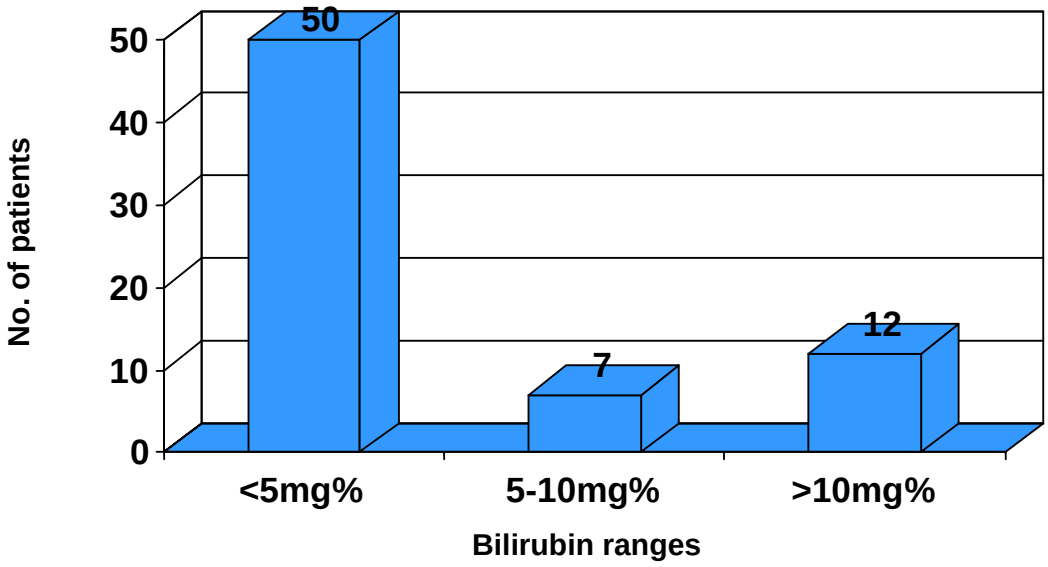
RESULTS

Between 1995 and 2008,sixty nine patients who underwent curative resection for periampullary carcinoma out of 81 patients who underwent pancreaticoduodenectomy during the same period were analysed.Out of the 69 patients , 47(68.1%) had ampullary carcinoma,7(10.1%) had cholangiocarcinoma,10 (14.4%)had duodenal carcinoma.

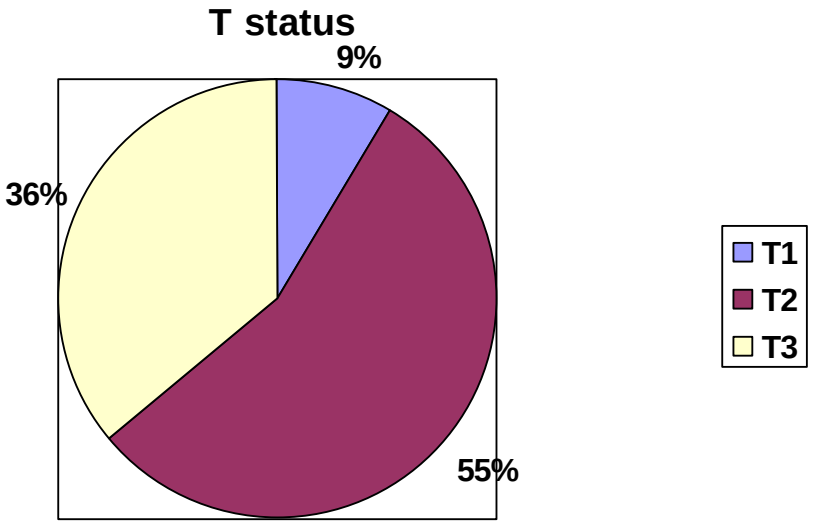
The median followup period was 39 months .The mean patient age was 52 years.39 (56.5%) were males and 30 (43.4%) were females .Jaundice was present in 56 patrients(81.1%).50(72.4%) patients had bilirubin < 5 mg%. Standard pancreaticoduodenectomy was done in 59 patients(85.5%) & PPPD in 10 patients (14.4%). The average blood loss was 1373 ml.The mean transfusion requirement was 2 units.The mean operating time was 6.1 hours. Major complications were present including pancreatic leak (13 patients) & biliary leak(5patients) in 18 patients (26%).Minor wound infections were present in 22 patients(31.9%).Delayed Gastric emptrying in 9 patients(13%).Relaporotomy was done in 4 patients(5.8%) indication being post operative haemorrhage..post operative mortality was 5.8%(4 patients).

The mean size of the tumour was 2 cm.23 patients(33.3%) had node negative disease and 46 patients(66.6%) had node positive disease.17.3% were grade I ,55% were grade II,27.5% were grade III tumours.

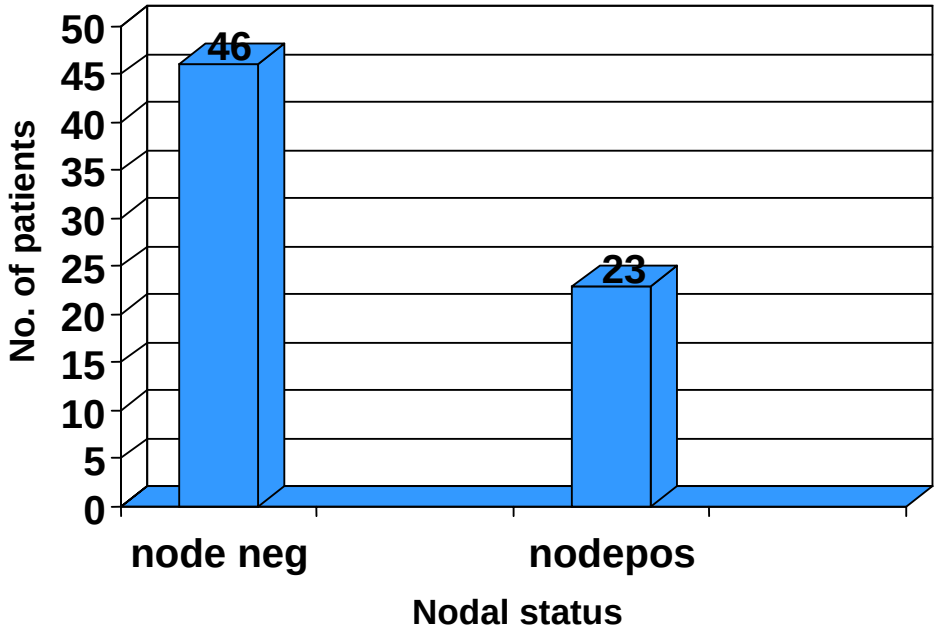
The distribution of serum bilirubin is as follows:



The distribution of T status is as follows:

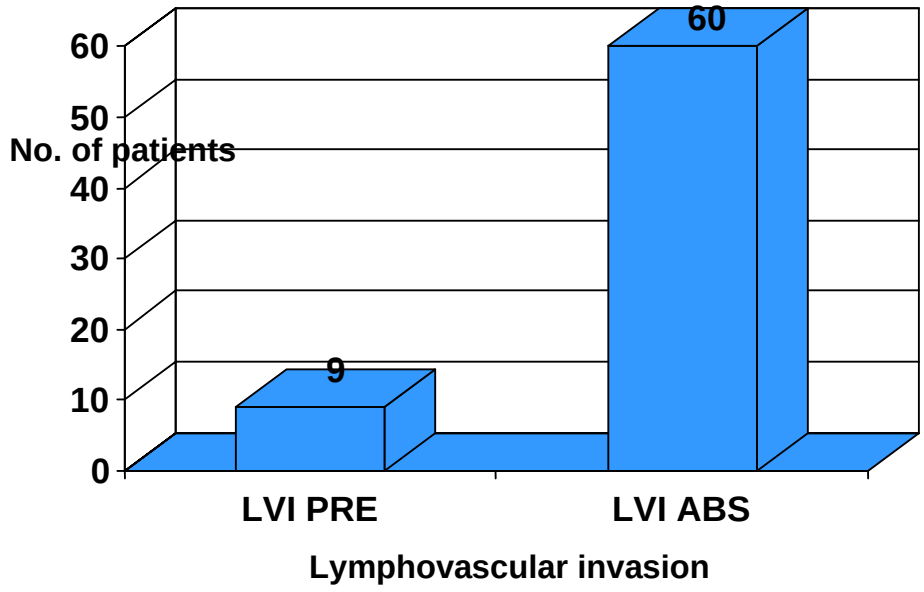


The distribution of nodal status is as follows:



(node neg- node negative,node pos- node positivity)

The distribution of Lymphovascular invasion is as follows:



(LVI-Lymphovascular invasion,LVI PRE –Lymphovascular invasion present,LVI ABS- Lymphovascular invasion absent)

TABLE 3 :

Results of univariate analysis of perioperative factors are shown in TABLE 3.

Variable		No. of patients	P value
Sex	Male	39(56.5%)	0.36
	Female	30(43.4%)	
Age	<50	26(37.7 %)	0.75
	>50	43(62.3%)	
Blood transfusion	yes	55(79.7%)	0.43
	No	14(20.2%)	
Preop bilirubin	0-4.99	50(72.4%)	0.0153
	5-9.99	7(10.1%)	
	>10	12(17.3%)	
Preop albumin	<3	11(15.9%)	0.34
	>3	58(84.05%)	
Preop Hb	< 10	10(14.4%)	0.29
	>10	59(85.5%)	
Preop Jaundice	yes	56(81.1%)	0.5
	No	13(18.8%)	
Preop biliary drainage	Yes	36(52.17%)	0.15
	No	33(47.82%)	
Complication	yes	34(49.27%)	0.46
	No	35(50.72%)	
Adjuvant chemotheraphy	yes	5(7.2%)	
	No	63(91.30%)	0.79
Blood loss	<1000ml	35(50.72%)	
	>1000ml	34(49.27%)	0.28

TABLE 4:

The univariate analysis of pathological factors for resected periampullary carcinomas are shown in TABLE 4.

Variable		No. of patients	P value
Size of the tumour	< 2 cm	38(55.07%)	1.0
	>2 cm	31(44.92%)	
T status	T1	6(8.6%)	0.01
	T2	38(55.02%)	
	T3	25(36.23%)	
Nodal status	Positive	23(33.33%)	0.0052
	Negative	46(66.66%)	
Grade	I	12(17.39%)	0.82
	II	38(55.07%)	
	III	19(27.53%)	
LVI	yes	9(13.04%)	0.02
	No	60(86.95%)	
Perinodal spread	yes	10(14.4%)	0.17
	No	59(85.5%)	
Site of tumour-	ampulla	52(75.36%)	0.62
	Duodenum	10(14.4%)	
	Distalbileduct	7(10.1%)	
No. of nodes positive	0	46(66.66%)	0.02
	1	8(11.5%)	
	2 or more	15(21.7%)	
Margin	Positive	3(4.3%)	0.69
	Negative	66(95.65%)	
Perineural spread	Present	(2.8%)	0.61
	absent	67(97.1%)	

By univariate analysis the following perioperative factors & pathological factors were analysed.The perioperative factors include age,sex,blood loss,blood transfusions,preoperative bilirubin (divided in to three groups – Group 1- 0.5 mg/dl,Group 2 – 5.1-10 mg/dl.Group 3 – above 10 mg/dl.),preoperative hemoglobin,preoperative albumin and surgical complications.The pathological factors include tumour size,T status ,stage of the disease,nodal status,number of positive nodes,grade of the tumour,Lymphovascular invasion,pericapsular spread.

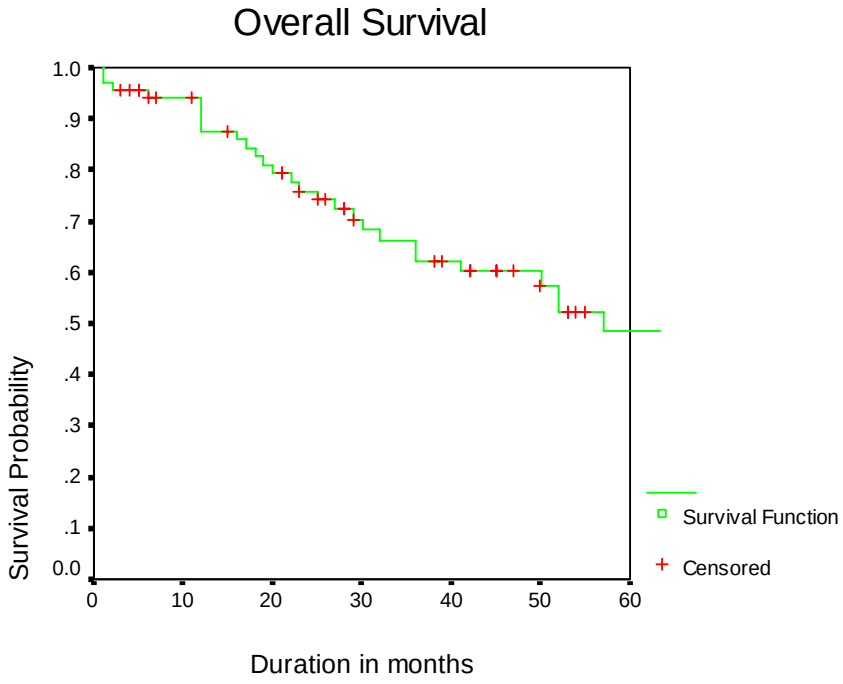
On univariate analysis preoperative bilirubin(high bilirubin range),T status , node positivity and Lymphovascular invasion were associated with a worse overall survival.On multivariate analysis preoperative bilirubin , Node Positive disease ,Lymphovascular invasion were associated with poorer overall survival.

TABLE 5:

Multivariate analysis of overall survival in resected periampullary carcinoma

Variable		**Hazard ratio(95% confidence interval)**	**P – value**
Preop Bilirubin	Group 1(0-5 mg/dl) Group 2(5.1-10mg/dl) Group 3(>10 mg/dl)	1 0.3(0.5-1.2) 2.9(1.2-7.1)	0.02
Nodal status	Node positive Node negative	1 3.0(1.2-7.5)	0.02
LVI	Present Absent	1 0.3(0.1-6.9)	0.04

Disease free Survival were 48.2%,76.5%,64.8% for ampullary,duodenal and cholangiocarcinomas.There was no statistical difference on comparing the three sites.20(28.9%) patients developed recurrence including 18 (26%) patients with distant recurrence.The 5 Year Overall survival for all patients was 47.8 % .



DISCUSSION

Previous reports suggest that patients with ampullary tumours have better survival than those with adenocarcinoma of the head of the pancreas(8).However ,reported series are small and often compiled over several decades.Over this period the diagnosis preoperative staging and treatment of periampullary tumours has evolved significantly.The present series report patients with periampullary tumour represents another large series from a single institution ,with 69 patients managed between 1995 and 2008.The 5 year survival rate after resection of periampullary carcinoma is 47.8%.The present 5 year survival rate is similar to most other large series in which the actuarial survival ranges from 34 to 45 %(8,10,91,92).Some reports presented even higher 5 year survival rates between 55 %and 61%(2,60,93,94). There are wide variations in median survival and the percentage of 5-year survivors, with the lowest survival figures generally coming from series dating back many decades. Nakase et al.(68) reported a 5-year survival rate of only 6%, which may have been negatively influenced by their data being derived from 57 different institutions. The operative mortality in this study was 16%, and high operative mortality appears to be a factor in the diminished survival reported in other series.Most of these studies include data from the 1940s to 1970s and therefore have not benefited from the improvements made in patient care over the past 2 decades.

During the current series there were no changes in the surgical procedure with regard to the extent of the resection or the lymph node resection, except for the shift towards pancreatico gastrostomy.Both classical pancreaticoduodenectomy and Pylorus preserving Pancreaticoduodenectomy has been performed.Both types of resection result in a comparable survival (39).

In this study,age ,sex,jaundice,blood loss,no. of blood transfusions,preoperative bilirubin ranges ,preoperative hemoglobin,preoperative albumin,preoperative biliary drainage , complications of surgery, adjuvant chemotheraphy were the perioperative factors taken for univariate analysis.Tumour size,T status,nodal status,grade,Lymphovascular invasion ,perinodal spread, margin status and perineural invasion were the tumour factors taken for univariate analysis. Preoperative bilirubin,T status,node positivity and Lymphovascular invasion predicted for improved survival by univariate analysis.Preoperative bilirubin ,node positivity and Lymphovascular invasion were independently correlated with survival in resected patients by multivariate analysis.

Several studies confirm the significant association of nodal metastases(63,90,93) tumor grade(2,66,59) and margin status(60)with patient survival. Others have found that tumorstage(2,60-62), tumor size(63) perineural invasion (25,64), lymphatic invasion,(2,25) venous invasion,(25)adjuvantchemotherapy(64) and blood transfusion(8) were significantly correlated with survival. Although a report from Johns Hopkins found blood transfusion, lymph node status, and tumor differentiation to be significant by

univariate analysis, none of these factors reached the threshold of significance by multivariate analysis(8).

In other studies that performed multivariate analysis , the only significant factor by multivariate analysis by Allema et al. was the margin of resection,(10) and by Monson et al(9) (after exclusion of nonampullary cases) was lymphatic invasion. In a smaller series of 28 resected patients,Neoptolemus et al.(2) found both tumor grade and tumor stage(where stage IV was defined as lymph node involvement) to be significant by multivariate analysis.For resected ampullary adenocarcinoma, several factors have been variably associated with survival(8,9,91,97) including tumor size, histologic differentiation, lymph node status,resection margin status, and perioperative blood transfusion.

A recent study interpreted high bilirubin levels as a sign of advanced stage by showing correlations with tumour related variables such as lymph node metastasis,pancreas and vessel invasion.(84).Bettschart et al, found that age and bilirubin concentration as two tumour independent factors predictive of survival in univariate analysis ,whereas a low bilirubin concentration favoured survival in multivariate analysis of the whole group(79).Few multivariate analysis have been performed to define non tumour related prognostic factors(8,69).Neoptolemos et al found no impact of bilirubin concentration ,but their series included only 22 patients undergoing Whipple's resection.(2).Berberat et al showed that high bilirubin negatively influences long term survival in non pancreatic periampullary

carcinomas.(81). The present study shows low bilirubin concentration favouring survival in both univariate and multivariate analysis.

Bettschart et al found that ,there was no significant difference in survival for patients with T 1 versus T 2 tumours.,wheareas T 3 tumours had a significant impact on survival.Poor differentiation was shown to affect survival in univariate analysis only(79).Berberat et al showed that extension of ampullary carcinoma into the pancreas (T3and T4) as a strong tumour related independent factor for survival .On univariate analysis low stage (T1,T2) and also absence of microscopic vessel invasion were associated with better survival.But multivariate analysis showed only low T status as an independent indicator of better survival in ampullary carcinomas.(81).Stiff et al showed that age,gender ,shape,degree of differentiation ,presence of vascular invasion were all found not significant.(7).The present study showed significant impact on survival of T 3 tumours compared to T1,T2 tumours on univariate analysis but not in multivariate analysis.Stage of the disease was found to be significant on univariate analysis but on multivariate analysis. Gender,tumour size, grade and pericapsular spread were not found to be significant factors for survival.

The incidence of nodal metastases ranges from 29% to 52%, with a mean of 40%(10,57).The presence of lymph node metastases proved to be a strong prognostic factor for survival in this study as in this study by Van Geenen et al(89).In ampullary carcinoma , the overall nodal status rather than the number of lymph nodes involved is the important factor associated with survival as in our study(87).However others

have shown that the number of nodes involved is of greater significance as a prognostic factor in addition to the overall nodal status when four or more nodes involved(87,95).In a series by Sommerville et al ,all patients with four or more nodes involved died of their disease within 29 months,with a median survival of 14 months(85).In the current series though the presence of two or more nodes was statistically significant by univariate analysis(p=0.02) ,it did not reach significance in multivariate analysis.The presence of positive lymph nodes was significant by univariate and multivariate analysis.

There is little agreement between published series as to which of these factors are the most important ,although lymph node positivity,tumour stage and perineural invasion are the factors most frequently cited.Stiff et al found that T stage ,N stage and the presence of perineural invasion to be significantly associated with a poorer outcome whereas age,shape ,degree of differentiation ,presence of vascular invasion, and blood transfusion requirements were not significant.(7).Bettschart et al showed that the most important factors for predicting survival were tumour related, such as pancreatic invasion,differentiation,perineural invasion and lymph node involvement.(79).The present study showed Lymphovascular invasion as a factor predicting survival in both univariate and multivariate analysis .

Several studies also reported tumour independent factors to be predictive of long term survival in multivariate analysis such as young age and absence of intraoperative transfusion.(79,83).Berberat et al ,showed surgical complications to be a strong indicator of shorter survival indicating safe surgical technique to be crucial

not only for the short term but also for the long term outcome of the patients.(81).Howard et al found , on multivariate analysis ,that tumor size,tumor grade ,post operative complications and resection margins were the most important co variables affecting survival,but that the absence of postoperative complications provided the most benefit in reducing the risk of dying from the disease(50).In the present study on analyzing the perioperative factors for impact on survival ,such as age,sex,blood transfusions,blood loss,preoperative bilirubin,preoperative hemoglobin,preoperative albumin and surgical complications,only preoperative bilirubin was found to be significant. In the present study,Age ,blood transfusions and surgical complications were not found to be significant factors as in other studies.

Recent studies in distal cholangiocarcinoma revealed much better survival with 27-41% 5 year survival rates (53,100,101).The small group of duodenal adenocarcinomas represent a rarity under gastrointestinal tumours.The few series reported in literature show a wide variation of 5 year survival rates from 20-75%(53,78,88).Berberat et al showed a 5 year survival of 50.5 %,29.9% and 24.5 % for ampullary carcinoma ,cholangiocarcinoma and duodenal carcinoma.The present study showed a 5 year survival rate of 48.2%,64.8%and 76.5% for ampullary, cholangiocarcinoma and duodenal carcinomas. If one looks at survival after resection, patients with duodenal cancer survivedlonger than those with ampullary cancer. One explanation for the observed patterns of survival in these periampullary tumors is that there are fundamental differences in tumor biology between these neoplasms.Whipple suggested that ampullary tumors were "better differentiated, of

the adenomatous type, slower to invade the lymphatics and blood vessels(46). Survival of patients with ampullary tumors generally followed closely behind those with duodenal tumors, whereas survival of patients with bile duct tumors generally fell between those with ampullary and pancreatic cancers. Perhaps periampullary tumors represent a biologic spectrum of malignancies, where intestinal-type tumors (like duodenal cancer) comprise the biologically more favorable end of the spectrum and pancreaticobiliary tumors the other.In the present study, patients with duodenal adenocarcinoma had a better survival followed by cholangiocarcinoma and ampullary carcinoma.

The morbidity associated with pancreaticoduodenectomy has decreased in recent years but remains substantial(64),ranging from 18 to 68 percent.(95).The major morbidity following pancreaticoduodenectomy in this study is 26 %. Post operative mortality was 5.8%.(4 patients).

CONCLUSION

Preoperative bilirubin , nodal involvement and Lymphovascular invasion are important predictors of survival in those who undergo resection of non pancreatic periampullary carcinoma.Ampullary tumours have a good prognosis, as they are often resectable .The acceptable morbidity rate among resected patients , support an aggressive surgical approach to the management of ampullary tumours.

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