

AMPULLARY ADENOCARCINOMA: DIAGNOSTIC AND THERAPEUTIC CHALLENGE

By

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Ampullary carcinoma is an entity of the periampullary tumors that have better resectable and survival rates. This study was carried out on 22 patients proved to have malignant ampullary region tumors .The study aimed at assessment of the different preoperative diagnostic procedures; study the incidence of operability of the tumors and evaluation of the different types of surgical palliative procedures with the least interference and the best palliation.

Keywords: Ampullary tumours- ampullectomy- duodenopancreatectomy-periampullary tumours.

INTRODUCTION

Carcinoma of the extrahepatic biliary tract has always been associated with a dismal prognosis. This is essentially the result of the slow and asymptomatic growth of the neoplasm that infiltrates the surrounding structures, such as the portal vein and hepatic artery, making a curative surgical treatment almost impossible ⁽¹⁾. However in the last decade, improvements in diagnostic, surgical, anesthetic, and intensive care techniques have allowed earlier diagnosis, to ameliorate the general condition of the patient, and thus offering a wider range of surgical options⁽¹⁾. The periampullary area is anatomically complex, representing the junction of three different epithelia: the pancreatic, bile ducts and the duodenal mucosa ⁽²⁻⁴⁾. With tumor growth, the epithelium of origin is often impossible to determine macroscopically, and these tumors are all classified as periampullary tumours ⁽⁵⁾. Early diagnosis of periampullary carcinoma requires a high index of suspicion and appropriate aggressiveness in pursuing the diagnosis ⁽⁶⁾. Ampullary carcinoma is an entity of the periampullary tumors that have better resectable and survival rates.

PATIENTS AND METHODS

This study was carried out on 22 patients proved to have malignant ampullary region tumors, who were

admitted to The Hepato-pancreatico-Biliary Unit, Department Of Surgery, Alexandria Main University Hospital during the period from April 2000 to December 2001. A patient with ampullary tumour presented to us in the same period of the study. She was a 72 years old female with dilated cardiomyopathy. She was a bad surgical risk patient and was palliated by papillotomy and stenting. She was not included in the study.

The study aimed at assessment of the different preoperative diagnostic procedures; study the incidence of operability of the tumors and evaluation of the different types of surgical palliative procedures with the least interference and the best palliation.

Patients in this study were subjected to history taking, physical examination, and full laboratory investigations. Tumor Markers in the form of Carcino-embryonic antigen (CEA), Carbohydrated antigen 19.9 (CA 19.9) were measured in all patients. Abdominal ultrasonography and Computed Tomography (C.T) were done in all patients. Endoscopic Retrograde Cholangio-pancreatography (ERCP) was tried in all patients. Magnetic Resonance Cholangiopancreatography (MRCP) was done in some patients. Patients were prepared preoperatively by a third generation cephalosporin and vitamin K injections. Forced diuresis (by mannitol and intravenous fluids) was

instituted the day before surgery. Eight patients (36.36%) with an admission serum bilirubin level more than 20 mg/dl. had sphincterotomy during ERCP performance so that the degree of jaundice decreased even to normal bilirubin level before surgery. Patients proved to have ampullary tumor with no evidence of metastatic deposits and fit for surgery were subjected to "Whipple's procedure", while those who were in a critical general condition that could not withstand lengthy operations were subjected to local excision of the ampulla (ampullectomy) with safety margins plus septoplasty⁽⁶⁾. Patients with advanced malignancy were subjected to either simple loop hepatico-jejunostomy (modified Roux-en-Y) with stapled entero-anastomosis or choledocho-duodenostomy⁽⁶⁾.

RESULTS

This study was carried out on 22 patients, ten patients (45.45%) were males, and twelve patients (54.54%) were females. Their ages ranged from 45 to 74 years with a mean of 58 ± 9.52 years. Jaundice was the main presenting symptom in all the studied patients. Other presenting symptoms included; upper abdominal pain in six patients (27.27%), and recurrent attacks of fever with rigors in two patients (9.09%). On clinical basis, hepatomegaly was found in ten patients (45.45%). The gallbladder was clinically palpable (Courvoisier's law) in twelve patients (54.54%). Ascites was clinically detected in two patients (9.09%). (Table 1) shows the results of the laboratory work up. CEA and CA 19.9 were measured pre and post operative, and the results are shown in (Table 2)

Ultrasonography of the abdomen revealed intra and extrahepatic bile duct dilatation in all patients (100%); with a diameter of the C.B.D ranging from 12 mm to 26 mm with a mean of 19 ± 9.89 mm. No hepatic focal lesion(s) was found in the studied patients. The lesion could not be visualized by ultrasonography. Computed tomography examination revealed dilated intra-hepatic as well as extra-hepatic biliary radicals in all patients (100%). In only five patients (22.7%) C.T could detect ampullary lesions. ERCP was attempted in all patients (22 patients) (Fig. 1). Eighteen patients (81.81%) revealed ampullary mass with variable appearance; punch biopsies were taken from these lesions which proved to be adenocarcinoma. The remaining four patients (18.18%) refused the procedure from the start. For these patients MRCP was done. Another 6 patients were referred to us with MRCP giving a total of 10 patients (45.45%) undergoing this procedure. MRCP revealed ampullary lesion in six patients (60%) (Fig. 2). Lower third common bile duct stricture in two patients (20%). It misdiagnosed ampullary tumors as being distal impacted stones in 2 patients (20%) (Fig. 3). (Table 3) shows the sensitivity of each diagnostic tool in defining the lesion.

Diagnostic laparoscopy was done in six patients who were highly suspected to have metastatic disease evidenced by the CEA levels, the U/S and C.T. scan findings. Four of these patients proved to have liver metastases and peritoneal deposits; the other two were metastasis free and had local resection. Whipple's procedure was done in ten patients (45.45%) successfully. Local excision with septoplasty was done in eight patients (36.36%) (Figs. 4, 5). Palliative procedures were done in four patients (18.18%) due to metastatic disease. Hepatico-jejunostomy with entero-anastomosis- modified Roux-en-Y- in two patients, and choledocho-duodenostomy in the other two patients. (Table 4) compares the operative time for Whipple's procedure versus the local resection.

In eight patients with liver cirrhosis and bad general condition local resection was done. Lengthy procedures were considered risky in these patients. The tumor was excised with a good safety margins in four patients. These patients did not require any further treatment, and by the end of this study, 26 months after resection they were tumor-free as indicated by normal levels tumor markers, follow up U/S and C.T. scan. Four patients had an excision, but unfortunately without negative safety margins. These patients were submitted to chemo-radiotherapy. Tumor recurrence occurred in two patients within six months with aggressive nature and they died two and three months later. The other two patients with positive safety margins for malignancy had tumor-free survival up to 24 months. Follow up U/S, C.T. scan, and laboratory investigations (mainly liver functions and tumor markers), revealed normal values in the six surviving patients. Two patients who underwent local excision complained of vomiting during their follow up. They had recurrence of the tumor with obstruction of the second part duodenum that necessitated gastro-jejunostomy.

Ten fit patients were subjected to the classical "Whipple's procedure" with pancreatico-jejunostomy done by the dunking method. Recurrent attacks of ascending cholangitis was experienced in four patients, they were controlled by antibiotic cover. Fatal pulmonary embolism occurred in two patients. It occurred on the ninth and tenth postoperative days. Hepato-renal syndrome occurred in two patients with a total operative mortality in four patients. Minor pancreatic leak occurred in one patient, who had Whipple's procedure. This happened seven days after operation and as treated by total parenteral nutrition and nothing per mouth for seven days.

Palliative bilio-enteric bypass was done in four patients due to metastatic disease. These patients survived for a mean period of eight months after surgery (6-10 months) without morbidity. (Table 5) shows the different complications which were recorded in the studied patients.

There was no statistically significant difference between Whipple's procedure and local excision as regards

survival. (Table 6) shows the survival of patients after treatment.

Table (1): different values of lab. Work up of the studied patients.

	<i>Total Bilirubin (mg/dl)</i>	<i>Direct Bilirubin (mg/dl)</i>	<i>SGOT (R&F)</i>	<i>SGPT (R&F)</i>	<i>Alk.Phosphatase (K&U)</i>	<i>Prothrombin Activity (%)</i>
Range	3-28	2-22	42-138	30-142	12-41	72-100
Mean	13.927	12.6	79.636	68.681	25.145	89.363
S.D.	6.271	7.080	31.363	31.510	10.140	10.082

Table (2): Tumor markers pre and post operative.

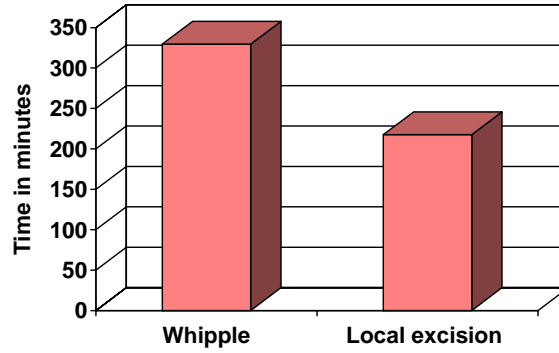
		<i>N = 22</i>		<i>Significance</i>
CEA	Preop.	Mean±SD	3.75±2.37 U/L	P=0.0262(NS)
		Range	0.8-7.6	
	Postop.	Mean±SD	2.72±1.42	
		Range	0.03-4.97	
CA19.9	Preop.	Mean±SD	761.72±912.99 U/L	P<0.0001(HS)
		Range	68-3360	
	Postop.	Mean±SD	2.57±1.55	
		Range	0.39-4.97	

Table (3) : Sensitivity of each diagnostic tool.

<i>Imaging Tool</i>	<i>Sensitivity</i>
ERCP	100%
MRCP	60%
Ultrasound	0%
CT	27.7%

Table (4): Operative time of the surgical resection procedures in minutes

	<i>Mean</i>	<i>Range</i>	<i>Significance</i>
Whipple Procedure	329.57±71	210-390	P=0.0158(NS)
Local excision	217.5±28.72	180-240	



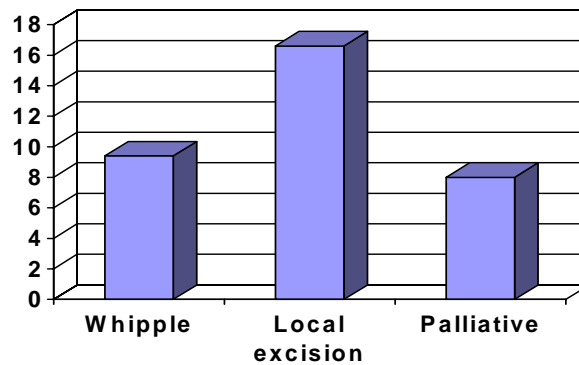
Duration of the operation in minutes

Table (5) : Complications of the studied patients.

<i>Morbidity</i>	<i>Whipple's operation (n=10)</i>	<i>Local resection (n=8)</i>
Vomiting	1 (10%)	2 (25%)
Minor pancreatic leak	1(10%)	0(0%)
Recurrent Cholangitis	4 (40%)	0 (0%)
Fatal Pulmonary Embolism	2 (20%)	0(0%)
Hepato-renal Syndrome	2(20%)	0(0%)

Table (6): Survival in the studied patients in months.

	<i>Number</i>	<i>Mean ± S.D</i>	<i>Range</i>	<i>Significance</i>
Whipple Procedure	10	9.4±10.8	1-24	P=0.3834 NS
Local resection	8	16.6±8.3	10-26	
Palliative procedures	4	8±1.7	6 - 10	



Survival in months



Fig. (1): ERCP showing a filling defect caused by an ampullary tumour.



Fig. (2): MRCP showing a filling defect caused by an ampullary tumour



Fig. (3): MRCP showing a distal filling defect caused by an ampullary tumour misdiagnosed as a stone



Fig.(4): An ampullary tumour seen after duodenotomy

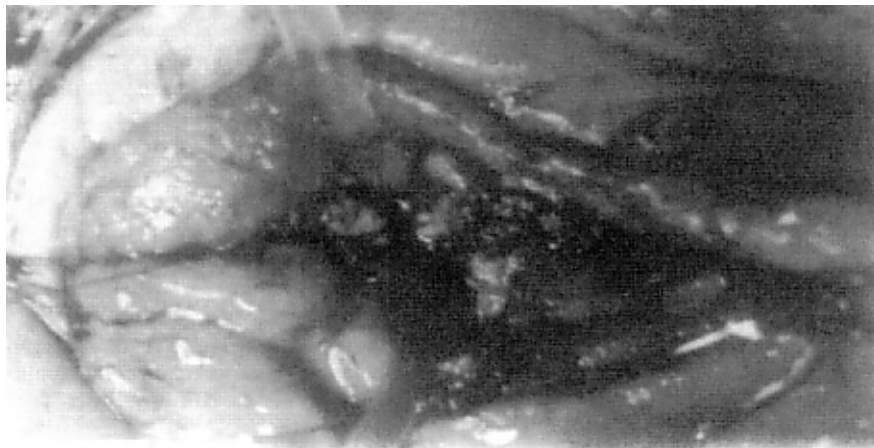


Fig. (5): Exision of the tumour and septoplasty with catheters in the CBD and pancreatic ducts.

DISCUSSION

The classification of tumors by the epithelium of origin depends on the skill and experience of the pathologist and is subjective. If it were possible to determine the epithelium of origin objectively and reproducibly in all ampullary carcinoma, this information could provide a better diagnostic guide-line⁽⁵⁾. CA 19.9 is the most useful marker for detection of Periapillary carcinoma⁽⁷⁻⁹⁾. In this study, patients who were submitted to surgical resection (Whipple's procedure or local excision with safety margins), the serum level of CA 19.9 returned to normal levels within one month after surgery, and started to increase again when patients developed recurrence. In surgical palliation patients, the CA 19.9 values did not decrease; it either remained as high as before surgery or even increased. The wide spread availability and use of ultrasound and computed tomography scanning, transhepatic cholangiography or ERCP, has correlated directly with earlier diagnosis⁽¹⁰⁾. Magnetic resonance cholangiography has been reported to detect the normal or dilated common bile duct in 96% to 100% of patients⁽¹¹⁾. A report by Zidi et al⁽¹²⁾ compared MRC and ERCP in a blinded fashion and found that, although MRC correctly classified stricture in 78% of patients, it underestimated tumor extension in 22% of cases. In our study U/S had an accuracy of 100% in detecting intra-hepatic bile duct dilatation. It could not visualize the ampullary lesion in any patient. ERCP showed an accuracy of 100% in defining the lesions. ERCP is a very good imaging tool in patients with jaundice, but it has an incidence of failure. It is also an invasive one carrying an incidence of complications. In the present study, MRCP had only a sensitivity of 60% in detecting the lesion. Misinterpretations occurred in four patients (two impacted stones, and two lower third common bile duct strictures). C.T. scan had a sensitivity of 50% in detecting the lesion. Liver secondaries and peritoneal seedlings are still difficult to diagnose by either U/S or C.T scan, particularly if these secondaries are small in size. Diagnostic laparoscopy enables direct visualization of small superficial liver secondaries, visualization of serosal seedlings, and minimal amount of ascitic fluid that could not be detected by other means of investigations. A major advantage of diagnostic laparoscopy is the assessment of operability, and resectability of the tumor. It may save patients from unnecessary laparotomy⁽⁶⁾. Although, we think that even if the patient had metastatic deposits in the liver or the peritoneum it is better to have bilio-enteric bypass than to have endoscopic stenting, with risk of stent obstruction and the need of frequent stent changing. Contemporary imaging studies used to evaluate periampullary carcinoma include endoscopic ultrasonography (EUS)⁽¹³⁾, helical (spiral) computed tomography (CT), and selective visceral angiography with portal venous phase (SVA)⁽¹⁴⁾. Helical CT scanning was found to be the single best preoperative

imaging study to determine resectability of periampullary carcinoma⁽¹⁵⁾. Currently, resectability is the only criterion needed to decide whether an aggressive operative approach (pancreaticoduodenectomy) or non operative treatment (biliary decompression) is indicated⁽¹⁵⁾. Patients with resectable tumors who are satisfactory operative candidates should be offered exploration and pancreatic resection. Patients with ampullary cancer have consistently realized 5 year survival rates between 25% and 40% following a radical resection, which is a higher survival than other periampullary tumors⁽¹⁶⁻¹⁹⁾. Interestingly, the long-term survival of selected patients with carcinoma of the ampulla does not seem to be influenced by the type of resection performed. The 5 year survival rates following local resection are not substantially different from this reported following radical resection^(18,19). A higher 5 year survival following local excision was noted by Wise et al⁽²⁰⁾, and Knox and Kingston⁽²¹⁾. This makes local excision a reasonable approach for treatment. This may be explained by the fact that local excision is only done for early tumors. Robertson et al⁽²²⁾ feel unable to recommend local excision, in view of the problems encountered except in older, higher risk patients unfit for major surgery. In this work, radical resection in the form of pancreatico-duodenectomy was done in ten patients (45.45%), local excision was done in eight patients (36.36%), while palliative bilio-enteric anastomosis was done in four patients (18.18%). The over all resectability rate in the ampullary tumors was 81.8%. The over all mean survival was 9.4±10.8 months for Whipple's procedure and 16.6±8.3 months for local excision. Despite the apparent longer survival after local excision, yet there is no statistical significance between it and Whipple's operation as regards survival. Local excision had its indication: 1) Poor general condition of the patients, 2) old age, and 3) border line state of the kidneys. The Whipple procedure is one of the most hazardous operations in the abdominal cavity. Surgeons who perform this operation therefore require not only the anatomical knowledge and technical skills but also the wisdom and judgment to assess the risk and benefits for each individual patient⁽²³⁾. Without adequate patient selection, mortality increases significantly from 6.1% of patients younger than 50 years to 76.6% of patients older than 70 years⁽²⁴⁾. An important point for postoperative recovery is the quality of the pancreatico-jejunoanastomosis. An anastomotic leak of the pancreatico-jejunoanastomosis occurs in 4% to 24% of patients and is a major factor for postoperative death in 7% to 73%⁽²⁵⁾. The incidence of pancreatic fistula or insufficient pancreatico-jejunoanastomosis is dependent on the quality of the pancreas⁽²⁶⁾. In patients with chronic pancreatitis and a remaining pancreas hardened by fibrogenesis with a dilated pancreatic duct, problems with the pancreatico-jejunoanastomosis were found in only 4-5% in contrast to 25% in those with a soft pancreas⁽²⁷⁾. In these high risk patients, somatostatin lowers the pancreas-related complication rate significantly,

as Fries et al ⁽²⁸⁾ found in a prospective randomized trial. Fistulas with no peritoneal signs healed under parenteral nutrition and, if necessary, with somatostatin ⁽²⁸⁾. Nowadays, most anastomotic leaks are well controlled with drains placed intra-operatively ⁽²⁹⁾. In the past, leak at the pancreatico-duodenectomy proved to be fatal in 10% to 40% of patients because of uncontrolled sepsis ⁽³⁰⁾, whereas nowadays the mortality has decreased much to 0% to 8% ⁽³¹⁾. Pancreatico-gastrostomy has been used as an alternative to pancreatico-jejunal anastomosis to decrease leakage incidence, and have been gaining acceptance by pancreatic surgeons ⁽³²⁾. In our patients, the incidence of pancreatic leak was (9.09%), which is within the range of the recent literature. With the recent development of sophisticated diagnostic aids permitting early diagnosis, local resection is suspected to have a greater role in the treatment of ampullary carcinoma in a few years time.

REFERENCES

1. Cubertafond P, Grainant A, and Cucchiario G. Surgical treatment of 724 carcinomas of gallbladder. *Ann Surg*. 1994; (219): 275-80.
2. Anderson JB, Cooper MJ, Williamson RCN. Adenocarcinoma of the extrahepatic biliary tree. *Ann R Coll Surg Eng* 1985; 67: 139-43. Quoted (15).
3. Dawson PJ, Connolly MM. Influence of site or origin and mucin production on survival in ampullary cancer. *Ann Surg* 1989; 210: 173-9.
4. Blumgart LH, Kennedy A. Carcinoma of the ampulla of Vater and duodenum. *Br J Surg* 1973; 60: 33-40.
5. Monson JRT, Donohue JH, McEntee GP, Mellrath DC, Van Heerden JA, Sharter RG, Nagorney DM, and Ilstrup DM. Radical Resection for carcinoma of the ampulla of Vater. *Arch Surg* 1991; 126: 353-7.
6. Yeo CJ, Cameron JL. Tumors of the gallbladder and bile ducts. In : Maingot's Abdominal Operations, Zinner MJ, Seymour I, Ellis SH (eds.), 10th ed. New York, A Simon & Schuster Company 1997 ; 1835 - 54.
7. Chalasani N, Balujul A, Ismail A, et al. Cholangiocarcinoma in patients with primary sclerosing cholangitis: a multicenter case-control study. *Hepatology* 2000, 31: 7-11.
8. Nichols JC, Gores GJ, La Russo NF, et al: Diagnostic role of serum CA19.9 for cholangiocarcinoma in patients with primary sclerosing cholangitis. *Maya Clin Proc* 1993; 68: 874-9.
9. Ramage JK, Donaghy A, Farrant JM, et al: Serum tumor markers for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. *Gastroenterology* 1995; 108: 865-9.
10. Tompkins RK, Saunders KY, Roslyn JJ and Longmire E Jr. Changing patterns in diagnosis and management of bile duct cancer. *Ann Surg* 1990; 211(5): 614-21.
11. Barish MA, Yucel EK, Ferrucci JT. Magnetic resonance cholangiopancreatography. *N Engl J Med* 1999; 341: 258-64.
12. Zidi SH, Prat F, Le Guen O, et al. Performance characteristics of magnetic resonance cholangiography in the staging of malignant hilar strictures. *Gut* 2000, 46: 103-6.
13. Rosch T, Braig C, Gain T, et al. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography: Comparison with conventional sonography, computed tomography, and angiography. *Gastroenterology* 1992; 102: 188.
14. Dooley WC, Cameron JL, Pitt HA, et al. Is preoperative angiography useful in patients with Periapillary tumors? *Am Surg* 1990; 211: 649.
15. Howard TJ, Chin AC, Sterib EW, Kopecky KK, and Wiebke EA. Value of Helical Computed Tomography, Angiography and Endoscopic ultrasound in determining resectability of Periapillary carcinoma. *Am J Surg* 1997; 174: 237-41.
16. Neoptolemos JP, Talbot IC, Carr-Locke DL, et al. Treatment and outcome in 52 consecutive cases of ampullary carcinoma. *Br J Surg* 1987; 74: 957-61.
17. Warren KW, Choe DS, Plaza J, Relihan M. Results of radical resection for Periapillary cancer. *Ann Surg* 1975; 181: 534-9.
18. Nakase A, Matsumoto Y, Uchida K, Honjo I. Surgical treatment of cancer of the pancreas and the Periapillary region: cumulative results in 57 institutions in Japan. *Ann Surg* 1977; 185: 52-7.
19. Van Heerden JA, Mellrath DC, Ilstrup DM, Weiland LH. Total pancreatectomy for ductal adenocarcinoma of the pancreas: an update. *World J Surg* 1988; 12: 658-62.
20. Wise L, Pizzimbono C, Dehner LP, Periapillary cancer. A clinicopathological study of sixty-two patients. *Am J Surg* 1976; 131: 141-8.
21. Crile G, Ibister WH, Hawk WA. Carcinoma of the ampulla of Vater and the terminal bile and pancreatic ducts. *Surg Gynecol Obstet* 1970; 131: 1052-4.
22. Robertson JFR, Imrie CW, Hole DJ, Carter DC, and Blumgart LH. Management of Periapillary carcinoma. *Br J Surg* 1987; 74: 816-9.
23. Sung JP, Stewart RD, O'Hara VS, Westphal KF, Wilkinson JE, and Hill J. A study of forty nine consecutive Whipple Resections for Periapillary Adenocarcinoma. *Am J Surg* 1997; 174: 6-10.
24. Lieberman MD, Kilburn H, Lindrey M, Brennan MF: Relation of perioperative death to hospital volume among patients undergoing pancreatic resection for malignancy. *Ann Surg* 1995; 222: 638-46.

25. Bakkevold KE, Kambestad B. Morbidity and mortality after radical and palliative pancreatic cancer surgery: risk factors influencing the short-term results. *Ann Surg* 1993; 217: 356-9.
26. Grace PA, Pitt HA, Tompkins RK, Den Besten L, Longmire WP. Decreased morbidity and mortality after pancreaticoduodenectomy. *Am J Surg* 1986; 151: 141-9.
27. Böttger TC, and Junginger T. Factors influencing morbidity and mortality after pancreaticoduodenectomy: Critical analysis of 221 resections. *World J Surg* 1999; 23: 164-72.
28. Friess H, Beger HG, Sulkowski U, Becker H, Hofbauer B, Denmler HJ, Buchler MW. Randomized controlled multicentric study of the prevention of compliance by octreotide in patients undergoig surgery for chronic pancreatitis. *Br J Surg* 1995; 82: 1270-9.
29. Cullen JJ, Sarr MG, Ilstrup DM. Pancreatic anastmotic leak after pancreaticoduodenectomy: incidence, significance and management. *Am J Surg* 1994; 168: 295.
30. Hester FP, Cooperman AM, Ahlborn TN, Antinori C. Surgical experience with pancreatic and Periampullary cancer. *Ann Surg* 1982; 195: 274.
31. Nitecki SS, Sarr MG, Colby TV, Van Heerden JA. Long term survival after resection for ductal adenocarcinoma of the pancreas: is it really improving? *Ann Surg* 1995; 221: 59.
32. Stephen O'Neil, Pickleman J, Aranha G. Pancreatico-gastrostomy following pancreaticoduodenectomy: Review of 102 consecutive cases. *World J Surg* 2001; 25: 567-571.