

# Treatment of Periapillary Neoplasms: Personal Experience and Review of the Literature

F. Stipa, G. Lucandri,  
M. Cavallini, B. Randone,  
V. Ziparo, S. Stipa

III Department of Surgery Hosp.  
S. Giovanni-Addolorata, Rome;  
I Department of Surgery,  
University "La Sapienza",  
I Department of Surgery, V.le del  
Policlinico, Rome, Italy

Depending on personal experience of treatment (245 patients) and literary data concerning periampullary neoplasms authors demonstrate that:

- pylorus preserving pancreaticoduodenectomy is good technique with better physiological outcomes,
- pancreaticogastrostomy has the same results of pancreaticojejunostomy,
- selfexpanding stent is useful paliative tool. Gastrojejunostomy is rarely necessary,
- radiochemotherapy increases median survival,
- long term survival has not improved in the last years.

## Introduction

Periapillary tumors have increased in frequency all over the western world, but recently this has not happened any longer. It remains the great surgical problem: only 10–15% of the patients can be considered operable after a careful study but the resection is possible in a decreased number. When the operation is performed by surgeons with good experience, the mortality is now less than 5% [1–3].

Recently it has been demonstrated that radiochemotherapy increases median survival and hospital volume strongly influences postoperative complications and long term survival. We are reporting our experience and reviewed the significative literature in the last years to clarify the study of the patients, the surgical technique, the survival and the use of neoadjuvant and adjuvant therapy.

## Personal Experience

From 1971 to 1999, we observed 245 patients with periampullary neoplasms, 155 males (63%) and 90 females (37%) with an average age of  $62 \pm 11.9$  years. Tumor arised from head of the pancreas in 173 patients (73%), ampulla of Vater in 38 (16%), biliary tract in 22 (9%) and duodenum in 4 (2%). Four patients with neuroendocrine tumors and 4 cisto adenocarcinomas have been excluded from the present analysis. On Table I patients are examined according to TNM staging system. Among 237 observed patients, a resection has been performed in 121 cases (51%), a palliative procedure in 101 (43%) and an explorative laparotomy in 15 (6%). Resectability rates are 68/173 (39.3%) for pancreatic adenocarcinoma (ADC), 33/38 (86.6%) for ampullary neoplasms, 17/22 (77.2%) for biliary tumors and 3/4 (75%) for duodenal tumors. By considering our experience in 3 different periods (1971–1977, 1978–1987 and 1988–1999) we observe resectability rates of respectively 34%, 47% and 61%. Radical procedures were a pancreaticoduodenectomy (PD) in 98 patients (81%) and a total pancreasectomy (TP) in 23 (19%). Among TP we include 7 cases in which pancreatic tail, after ex-vivo irradiation, has been reimplemented in Scarpa's triangle, using femoral vessels for anastomosis. Palliative procedures were 7 tumorectomies (7%),

39 bilio-digestive anastomosis (cholecysto-gastrostomy 19 cases, choledoco-duodenostomy 11 cases, cholecysto-jejunostomy 6 cases and hepatico-duodenostomy 3 cases) (38%), 40 associated biliodigestive and gastro-enteroanastomosis (cholecysto-gastrostomy 22 cases, choledoco-duodenostomy 11 cases, cholecysto-jejunostomy 5 cases and hepatico-jejunostomy 2 cases) (39%), 5 gastroenteroanastomosis (5%), 12 biliary drainage procedures (11%), external in 9 cases, internal-external in 2 cases and an internal selfexpanding stent in 1 case. Gastrointestinal progression has been restored by using gastric resection with TL oral antecolic gastrojejunostomy in 67 cases (55%) or pilorus conservation with Traverso's procedure in the remaining 54 (45%). Treatment of pancreatic stump has been a TT anastomosis with jejunum in 49 cases (46%), a TL anastomosis with jejunum in 35 cases (33%), occlusion of pancreatic duct in 13 cases (12%), auto-transplantation of the pancreatic tail in the Scarpa's triangle in 7 (7%) and drainage of the duct without intestinal anastomosis in 1 case (2%). In pateints with soft pancreatic tissue and small pancreatic duct we firstly performed an autotransplantation of the pancreatic tail after ex-vivo irradiation (20–30 Gy). Femoral vessels have been used for revascularization. After that we preferred the closure of the pancreatic duct with Tissulcol (12 cases) and suture of the pancreatic stump. It has been drained using 2 laminar tubes, above and below the operative field. A spontaneus fistula has been always appeared, but it healed after 40–60 days. Patients has been always treated p. o. with octreotide (0.05 mgr. X 3 s. c.). Mean follow up is  $31 \pm 48$  months and  $8 \pm 8$  months respectively for pancreatic ADC submitted to radical or palliative procedure,  $52 \pm 51$  months for patients with ampullary neoplasms and  $29 \pm 24$  months for patients with choledocal tumors. Twelve patients were lost at follow up.

Overall operative mortality was 20% (48/239); in the last decade personal mortality has been 4.7% (1/21). After radical procedure it was 22% (27/121) and after palliative operation it was 18% (18/103). Among resective operations mortality was 18% after PD (18/98) and 39% after TP (9/23); among PD mortality was 25% (14/55) in the Whipple's procedure and 9% (4/43) in the Traverso's procedure. Post-operative

Tumor staging						
	1	2	3	4a	4b	n.s.
Pancreas	12 (7%)	14 (8%)	38 (22%)	44 (25%)	48 (27%)	17 (11%)
Ampulla	11 (29%)	18 (47%)	8 (21%)		1 (3%)	–
Choled.	6 (27%)	5 (23%)	5 (23%)	5 (23%)	1 (4%)	–
Duod.	2 (50%)	–	2 (50%)	–	–	–

complications were: anastomotic leakage in 6 cases (33%), hemoperitoneum in 4 (16%), acute renal failure in 3 (16%), pulmonary embolism in 2 (11%), gastro-jejunal leakage, jejunal bleeding, and respiratory failure 1 case each. After TP operative mortality has been due to sepsis in 4 cases (45%) (2 due to biliary fistula), acute renal failure in 2 cases (22%), acute respiratory failure, jejunal bleeding and gastro-jejunal leakage 1 case each (11%). As regard autotransplantations, we observed 1 p. o. death due to sepsis after removal of necrotic tissue. In 2 cases vascular complications required removal of the pancreatic tissue. Mean survival of transplanted patients has been 14 months (range 2–43), while mean survival of the transplantation has been 10 months, with a maximum of 19. One patient presented and undifferentiated ADC in the transplanted tissue after 43 months. Mean time for closure of the pancreatic fistula after using of Tissucol was 60 days (range 49–78). Among p. o. complications, pancreatic fistula occurred in 22 patients (22/98, 22%). For patients radically operated, 5-year actuarial survival rate is 12% in pancreatic tumors, 33% in ampullary tumors, 0% both for choledocal and duodenal tumors (Figure). In patients submitted to palliative procedures for pancreatic ADC, 1-year survival was 15%, 3-year survival was 1% and 5-year was 0%, while periampullary survival at 1, 3 and 5 year was respectively 68, 49 and 33%.

## Discussion

### Study of the patients

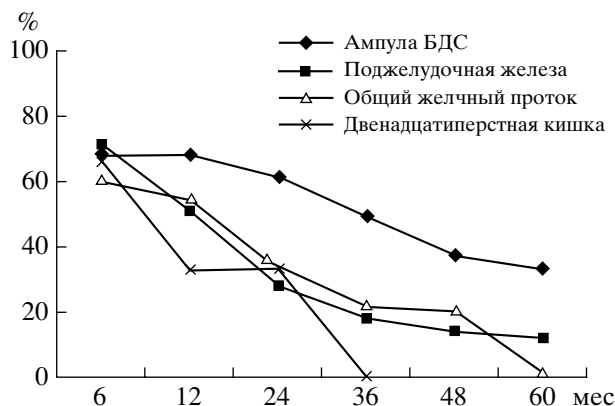
Islet Amyloid Polypeptide (IAPP) is found in 90% of patients with non insulin-dependent diabetes mellitus and in 80% of patients with pancreatic cancer [4]. IAPP can be used for early diagnosis of this cancer because diabetes often precede pancreatic cancer.

Mutation of *K-ras* oncogene are also found in 80% of patients with ductal pancreatic cancer and in low grade premalignant conditions like mucinous ductal ectasia as carcinoma *in situ* [5]. IAPP and *K-ras* together can be useful to make early the diagnosis of ductal carcinoma.

Dynamic contrast enhanced CT plus laparoscopy staging can predict resectability in 90% of the patients and prevents laparotomy for the patients who would not benefit from an operation [6]. Helical CT has demonstrated better than conventional CT [7].

The study of bone marrow is very important. With monoclonal antibodies against epithelial cytocheratins (CKS) is possible the detection of even single disseminated cells. In 42 patients with pancreatic cancer more than 50% were found with tumor cells in bone marrow. In 24 patients with follow up of 16 months after pancreaticoduodenectomy, 79% with CKS-positive cells in bone marrow, developed metastases or local recurrence. None of the patients without cells in bone marrow had any sign of relapse [8]. The study of peritoneal washing to discover free cancer cells is very important. The last study report a incidence of 7% of patients with resectable tumors after careful preoperative assessment [9].

It was demonstrated no relation with previous percutaneous fine needle aspiration cytology (FNAC) [9]. Another study report a incidence of 17% [10]. It is now believed that the presence of free peritoneal cells in connection with FNAC is related with a bad prognosis as was demonstrated by Warshaw [11]. Preoperative FNAC or transcuteaneous biopsy with cutting needle has been performed by several surgeons [12] with preference for FNAC because consistent malignant diagno-



Patients at risk	Patients at risk						months
	0	6	12	24	36	48	
68	47	33	24	9	7	6	Поджелудочная железа
33	20	20	18	14	10	8	Амплитуда БДС
17	10	8	4	3	2	–	Общий желчный проток
3	2	1	1				Двенадцатиперстная кишка

Periampullary neoplasms: actuarial survival.

Периампулярные опухоли: актуарная выживаемость.

sis assumed with cytology was better than with histology and insufficient material was more common for histology. Intraoperative FNAC, direct wedge biopsy or trough WIM-SILVERMAN and trucut needle have also been rather often used. For suspected deep tumors in the head of the pancreas is better to use the needle. The most important decision is the necessity of the FNAC preoperative or intraoperative biopsy. We agree with Ihse [12] that in centers with low operative mortality is not necessary because chronic pancreatitis is an accepted indication for resection when the head of the pancreas has clear signs and symptoms of biliary obstruction. On the other hand, if preoperative chemotherapy is planned, there is need of cancer diagnosis. Pancreatic preoperative biopsy is also needed in patients with unresectable lesion in whom radiochemotherapy is planned. We have also to remember that false negative results are always present.

Comparison between laparoscopy, laparoscopic ultrasonography (LapUS), transabdominal ultrasonography (USS), contrast-enhanced computer tomography (CT) and selective visceral angiography have been recently made in 50 patients with periampullary tumor. LapUS was better than USS and CT regarding metastases and the difference was statistically significant, but from this point of view was sufficient laparoscopy, because the metastases are all superficial. Laparoscopy with LapUS was the best method for assessing resectability. No method was able to give accurate demonstration of N-staging [13].

There was still a problem because it was not used helical CT, which is clearly superior to standard CT and the endoscopic ultrasonography. Positron Emission Tomography (PET) is based on enhanced glucose metabolism by pancreatic cancer. Using 2-(18F)-Fluoro-2-Deoxy-D-Glucose, PET can diagnosis pancreatic cancer and differentiate this from chronic pancreatitis. It has a sensitivity of 85–98% and a specificity of 53–93%. High sensitivity and high specificity are dependent on stage of the tumor [14]. Sensitivity to detect lymphnode metastasis is around 65%, which is clearly better than CT and US [15].

Magnetic Resonance Cholangiopancreatography with the last apparatus allows images with a duration of a breath hold without the use of i. v. contrast. Total room time can be less than 10 minutes. If the technique is superior to the other standard diagnostic studies previously reported is not clear [16]. But has been used by many authors [17–19].

Intraoperative study with intravascular ultrasonography (IVUS) can be very important to define invasion of portal vein [20, 21]. The examen, performed with an apparatus of 8 F diameter catheter is entered in a branch of the superior mesenteric vein. In the study by Nakao *et al.* [22] the examen was performed in 45 patients with tumors of the head of the pancreas. The accuracy of IVUS was statistically superior to portography and CT (94.5% vs 70.9% and 78.1% respectively). The 2 false positive results with IVUS were in patients with severe pancreatitis around the tumor.

### Preoperative treatment

There is now evidence that preoperative biliary intubation does not improve surgical results [23] and increase the incidence of bile contamination and postoperative complications [24].

### Techniques

Some authors [25, 26] believe that pancreaticogastrostomy is safer than pancreaticojejunostomy, to prevent pancreatic fistulae. Finally a trial with 145 patients with malignant and benign disease operated upon by pancreaticojejunostomy and pancreaticogastrostomy had the same incidence of pancreatic fistulae (11% vs 12% respectively) [27].

Pancreaticoduodenectomy preserving the pylorus (PPPD) is considered by many surgeons to be a better technique. The operative time is shortened [28], the morbidity and the mortality are the same which can be observed in patients with gastric resection [29, 30]. The real advantage is the better nutritional recovery. A problem connected with PPPD is the infiltration of the duodenal margin and incomplete removal of the regional lymphnodes [28, 29]. A frozen section of the duodenal margin can be performed and of the answer is positive a gastric resection has to be performed [30]. Sharp *et al.* [31] have observed three patients with recurrence at the duodenal transection. This finding was never observed by other author [32, 33]. Nodes close to the pylorus can be removed and if nodes are found along the stomach (which can be observed in 14% of the patients [34] but not have found by Cubilla [35] and Ohta [36]) can also be removed.

As regards recurrence, the retroperitoneal tissue near or in contact with superior mesenteric artery is the most common involved site [37]. To avoid recurrence in this site is necessary to free the right margin of the artery. Recurrence is observed in the pancreatic bed in one third of the patients [38] but the extent of resection does not increase the survival.

The stage of the disease is so poor that anything we make it does not improve survival. TP is considered a better operation in tumors of the head of the pancreas because can avoid the pancreatic margin involvement, which is observed even in 20% of the patients [39], the fistulae and can remove multicentric disease [40, 41]. The operative mortality and morbidity were higher in comparison to PD [39]. Other authors found much lower mortality [40, 41]. In a multicentric study of 155 patients who had PD and 122 patients with TP, it was observed a minor survival in the second group. We have to consider that these patients had tumor of greater size [39]. We have performed TP in patients with friable pancreatic stump, which could cause a fistula more often, but the mortality was too high and we have abandoned the technique. In this situation treatment of pancreatic stump and remnant Wirsung with neoprene may be useful; Di Carlo *et al.* performed this technique on 51 patients, non suitable for jejunal anastomosis, and reported a 4% rate of p. o. pancreatic fistula [32]. We

had also another big problem regarding difficult diabetes, which has been observed but anyone we have used the technique [39].

Portal vein resection can be performed if on the basis of a complete preoperative study the patient is operable. Launois [42] has found that in 14 patients in whom he performed this resection, only in 3 was histologically proved the invasion of the vein. In the other patients adherence was only the result of inflammation. He found 14% 2 year survival compared to 34% in patients without portal vein resection. The experience of several surgeons [43, 44] reported a 3 year survival between 12 and 25%. A preserved venous allograft can be used to bridge a large defect of the portal vein, or a vascular prosthesis. If the portal vein tract is short a direct suture can be performed [45].

Extended lymphadenectomy has been performed by many surgeons [46, 47] but only recently two randomized study began to clarify the problem. A first randomized study compared 40 patients operated with standard lymphadenectomy and 41 operated with the extended technique; the operative mortality rate was similar (2 patients), without significant differences in hospital morbidity. An “*a posteriori*” survival analysis seems to demonstrate better result for patients submitted to extended lymphadenectomy ( $p < 0.05$ ), but few patients are included into the study to state definitive conclusions. Furthermore the difference between the mean number of resected nodes in the 2 groups (respectively  $13.3 \pm 8.3$  and  $19.8 \pm 1.1$ ) is not significant [48]. In the second randomized study by Yeo *et al.*, including 56 and 58 patients in the 2 subgroups, the mean number of resected nodes has been 16 and 27 respectively. No differences in mortality and 1-year survival have been detected since now; patients submitted to extended lymphadenectomy present a larger rate of delayed gastric emptying. This is a preliminary report and the authors will enrol 150 patients in both arms for definitive conclusions [49, 50].

Ampullary tumors may be treated with local resection or ampullectomy; it must be performed with at least 1 cm of free-resection margin, both from duodenal and from choledocal site. If o. histological examination confirms that resection has been radical, biliary and pancreatic ducts have to be reimplemented. This procedure has been indicated for benign ampullary lesions and for T1 tumors less than 3 cm in diameter [51]. We have to consider that in highly specialized center good results may be reached also with PD: in the Johns Hopkins experience (106 patients), the authors report a hospital mortality of 3.8% and a hospital morbidity of 38% [52]. In specialized centers ampullary neoplasms have to be technically treated like ductal carcinoma.

### Operative risk

The most important conditions predicting postoperative mortality following resection or palliative operations are systemic organ failure (cardiorespiratory or renal), age over 70 years or poor general conditions. Both

factors are required to have a significant impact. In patients older than 70 years but without systemic organ failure a resection with same postoperative mortality and survival similar to those of younger patients can be obtained [53].

### Postoperative morbidity

The morbidity remains between 30% and 50% but the severity of complications and the mortality have decreased in a significant way. Anastomotic leak of pancreaticoenterostomy is between 8% and 19% [54]. Bile leaks are less than 5% [55]. The control of anastomotic leak is now obtained with good drainage at the operation. Even if the leak has to be directly treated, percutaneous technique under radiologic guidance can be used to solve the problem. Now the mortality due to sepsis consequent to the leak has decreased to 0–8% [56].

Postoperative gastrointestinal hemorrhage has also decreased very much (0–5%) [56] because the surgical technique has improved and there is the standard treatment with antacid drugs.

Delayed gastric emptying occurs in 23% to 35% of patients [55, 56] and is considered more frequent in patients with PPPD. Other surgeons disagree [57, 58] and a silent leak of pancreaticoenterostomy has to be considered as cause. Klinkenbijn [28] has proved that PPPD is faster than PD. If there is not this complication, delayed emptying is not a cause of mortality but only of prolonged hospitalization. Severe gastric ulceration was found in 2% to 18% in PD and in 0–19% of PPPD [59]. Studies on body weight gain after PPPD have been performed and in two experiences it was better after PPPD than after PD [32, 60]. The study of Horstmann [61] has demonstrated that it is better to perform the antecolic duodenojejunostomy instead of a retrocolic one. They also noted that in 36 patients with no postoperative complications delayed gastric emptying was observed in only one patient. In the 15 patients with complications, 5 (30%) had delayed gastric emptying ( $p = 0.002$ ). A study including only pancreaticoduodenectomy for malignant disease, did not show a statistically significant difference in pancreatic fistulae between the patients treated with octreotide and the control group [62]. To prevent delayed gastric outlet obstruction, Yeo *et al.* [63] demonstrated that erythromycin decreases delayed gastric emptying and this drug has to be used in all patients.

### Survival

Apparently the survival of pancreatic tumors has increased in the last decade, reaching 24% and 36% in 2 centers of large experience [54, 64]. The first group performed extended lymphadenectomy and the second the standard one. We have to be careful to judge these results because there is a big difference if we consider the overall and the actuarial survival. The first one, reported to 5 years means that all the patients had a follow up of 5 years and the second one had a limited length of follow up and the 5 year actual survival was

13% and not 36%. A better survival can also be a consequence of erroneous pathological study of the surgical specimen. In the Mayo Clinic [65] 12 of the 31 patients (39%) who had a diagnosis of ductal carcinoma and survived more than 3 years, review of an external pathologist demonstrated non ductal carcinoma. Actually the patient with this diagnosis had a mean survival of 54 months. Another group of surgeons [66] who re-studied pathologically the patients before reporting the experience, found that 17% had no cancer and 29% non ductal carcinoma. Only 11 of the 23 patients who survived 3 years had ductal cancer confirmed by the pathologist. In another center [67] the 5 year survival would have been increased from 10% to 19% if the pathologist did not reviewed. Five-year survival significantly differs according to tumor's stage, reaching 57% for stage I, 26% for stage II and 21% for stage III [64]. Ampullary, biliary tract and duodenal tumors present better 5- and 10-survival, respectively of 50 and 25, 30 and 21, 60 and 59% [54, 64, 67].

The actuarial 5 year survival in the recent literature is between 9 and 12% [1, 32, 33, 42, 54, 64]. If we divide the patients by stage we can have 5 year survival for stages I and II respectively of 13 and 36%, compared to 1 and 14% for stage III [64]. Small tumors, less than 2 cm have a survival which can reach a 20% rate [68]. Histologically negative resection margins have a better prognosis, 12 and 26 vs 0 and 8% [65]. When we have small tumors, with negative resection margins and no perineural and duodenal invasion, the survival can be 23% [65]. High tumor grade and aneuploidy are strong preoperative factors (8 vs 39% survival). Total pancreatectomy does not increase survival [69]. In the large experience of Yeo *et al.* [53] the multivariate analysis of the factors influencing survival has demonstrated that tumor diameter (>3 cm), intraoperative blood loss (>700 ml), positive resection margins and adjuvant radiochemotherapy are statistically significant. For positive resection margin we have to consider this fact at the pancreatic neck, the uncinate process, the bile duct, duodenum and retroperitoneal tissue. In this large experience the margin was negative in 71% of the patients. If the neck of the pancreas is positive at frozen section, a further resection has to be performed. The radiochemotherapy was 40–45 Gy on the pancreatic bed and two-three days of 5FU infusion, followed by weekly bolus 5FU for four additional months. In addition we recently demonstrated that angiogenesis is a prognostic factor independent from TNM staging in assessing patient's prognosis; so it could be useful in properly select patients suitable for additional treatments [70].

### *Palliative treatment*

Experiences have demonstrated comparable survival, need for hospitalization and cost for patients with endoscopic treatment compared to surgical bypass [71]. Recurrent jaundice and cholangitis was more frequent after stenting than after surgical bypass (respectively up to 38 and 10%) [72]. Deep self-expanding

metal stent is better than the plastic tube. They rarely migrate and are currently widely used; an improvement in quality of life has been demonstrated. Davids *et al.* performed a randomized study on 105 patients with unresectable distal bile-duct malignancy and treated with metal stents and plastic stents. They found a longer patency with the first ones and adequate palliation [73]. Nausea and emesis are reported in 30% of patients not operated upon, but is not always associated with gastric outlet obstruction. Probably this is caused by gastroparesis from a neurogenic disturbance. Real gastric outlet obstruction occurs in less than 10% of the patients with pancreatic adenocarcinoma [74]. In a recent study of 101 unresectable patients with carcinoma of head of pancreas, only 3 patients required a subsequent surgical procedure to treat biliary or gastric obstruction. One patient had biliary and gastric bypass and 2 only gastric bypass. Biliary obstruction was treated by endoscopic stent in the other patients [6]. When a surgeon performs biliary and gastric bypass has to consider the long hospitalization and the complications. They are observed in 18 and 25% of the patients respectively. Explorative laparotomy alone had complication in 12% of patients [74]. We believe that in patients with unresectable tumors of head of pancreas having a survival of 3–6 months [2] the biliary obstruction can be treated with endoscopic stent and the real documented gastric obstruction with gastric bypass. We have to remember that recurrent symptoms of obstruction are found in 7% of the patients treated prophylactically with gastrojejunostomy [75]. According to some authors the gastric bypass has to be performed antecolic and at least 12 cm in diameter [76]. A recent randomized trial, including 44 patients undergoing gastrojejunostomy and 43 who did not, demonstrated that prophylactic retrocolic gastrojejunostomy may be useful in prevent gastric outlet obstruction, avoiding a subsequent emergency procedure in 19% of patients [77]. In the postoperative period gastric proton pump inhibitors are indicated to prevent gastrointestinal bleeding.

Control of pain may be reached with surgical exeresis of the celiac trunk during palliative procedure or, whenever possible, by percutaneous alcoholic injection [78].

### *Neo-adjuvant and adjuvant treatment*

The Gastrointestinal Tumor Study Group has compared a control group with a group treated by combining radiotherapy (40 Gy) and 5FU. The two year survival was 15% and 42% respectively [79]. In a prospective study [80] was also demonstrated that radiotherapy and 5FU has a significative impact on survival. No randomized study has been done to demonstrate that combining 5FU with other drugs is better than 5FU alone. In any case monotherapy is less toxic than multitherapy. In a recent study [81] not randomized, postoperative intraarterial chemotherapy was compared with a control group. 24 patients entered in the first group and 25 in the second group. The infusion was for 5 days: 5FU, mitoxantrone, folinic acid and cisplatinum. The treatment was repeated at average of 5 times at monthly

intervals. With actuarial analysis of patients with RO resection the survival of 4 year was respectively 54 and 9.5% and statistically significant. The toxicity was acceptable but the patient has to be in bed for 5 days in each cycle. The local recurrence rate was the same as is reported in the literature (about 80%). But the recurrence in the liver was very low (17%). Survival in intrarterial and portal vein infusion of 5FU was reported as 54% at 5 year in 20 patients treated by Ishikawa [82]. These two studies are interesting but now need a randomized trial to accept them for any patient.

As regard intraoperative radiotherapy, in a trial performed by National Cancer Institute no improvement in survival was demonstrated with intraoperative radiotherapy (IORT), in comparison to external radiotherapy and 5FU [83]. Another trial [84] of the same Institute demonstrated a trend to better survival with IORT in comparison to no radiotherapy. Unfortunately the operative time is about 9 hours. Another study comparing IORT with external radiotherapy + 5FU [85] cannot be accepted because the selection of the patients is unclear.

Two trials on preoperative chemotherapy have shown that chemotherapy increases significantly survival in patients and ameliorates quality of life in patients with unresectable tumors. The treatment with chemotherapy was compared with a control group. The addition of Adryamicin [86] or hycanthone [87] to radiotherapy in comparison to radiotherapy and 5FU gave no improvement in survival and is more toxic.

Radiotherapy and chemotherapy mainly with 5FU has been performed in patients not operable, to downstage the lesion. Several studies reported a limited number of patients [88] with possibility to operate them with a good survival. Mitomycin C, cisplatin and 5FU have been injected in the celiac trunk, after a closure of the abdominal aorta with a balloon, above the liver. Tourniquet are placed around the thighs to block the circulation in the limbs. A strong regression in tumoral bulk has been observed but no data on survival has been until now reported [89].

No endocrine therapy with luteinizing-hormone releasing hormone and somatostatin or tamoxifen has showed any statistically significant survival [90, 91]. A controlled trial of Flutamide, a pure androgen receptor-blocking drug shows same promise in comparison to placebo [92]. Blood transfusion during operation can influence survival. It was demonstrated that patients who receive 2 or less units of blood survive longer than the patients with 3 or more units. Allema *et al.* [93] made similar observations. Probably the patients who need more transfusions have more difficult and extensive lesions. Postoperative total parenteral nutrition has to be avoided because is responsible of an increase of complications [94].

## Conclusions

- CT, laparoscopy and endoscopy are sufficient to study completely periampullary tumors. Ecolaparoscopy

is a useful addition but until now few hospitals can follow the experience.

- PPPD is a good technique with the same morbidity and mortality as the classical operation with gastric resection but better from physiological point of view.
- TP has the same long term results of PD but the consequent type of diabetes is dangerous.
- Pancreaticogastrostomy has the same results of pancreaticojejunostomy.
- Closure of Wirsung duct with neoprene is useful when the pancreas is not sclerotic.
- PD has to be performed by surgeons with large experience, otherwise the mortality is too high.
- resection of the portal vein can be performed with acceptable results.
- Palliative treatment can be done with selfexpanding metallic stents. Gastrojejunostomy is rarely necessary.
- Control of pain can be done with alcoholic injection.
- Adjuvant radiochemotherapy can be useful to increase the survival in tumor of pancreas.
- Long term survival has not really improved in the last years.

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