

ORIGINAL ARTICLE

Usefulness of follow-up after pancreatoduodenectomy for carcinoma of the ampulla of Vater

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Abstract

Background: The prognosis for carcinoma of the ampulla of Vater (CAV) is better than for pancreatic cancer. The 5-year survival median rate after resection of CAV is 45%, but late recurrences remain possible. Several survival factors have been identified (lymph nodes, perineural invasion), but few data are available on the type of recurrences, their impact and their management. **Patients and methods:** A total of 41 patients treated by pancreatoduodenectomy (PD) for CAV from 1980 to 2003 were studied retrospectively. Patient selection, long-term survival recurrence rate and recurrence treatment were reviewed. Univariate and multivariate proportional hazards analysis were conducted on this series. **Results:** The mean follow-up was 48 months. Five-year survival was 62.8%. Eleven patients had recurrences (6–67 months). Recurrence was associated with time to all-causes death (hazard ratio [HR] 4.3, $p=0.003$). Factors predictive of recurrence were perineural invasion (HR 5.3, $p=0.02$), lymph node invasion (HR 5.3, $p=0.02$) and differentiation (HR 0.2, $p=0.05$). Three patients underwent surgical R0 treatment of their recurrences. Two who presented with solitary liver metastasis are alive and disease-free. **Conclusions:** Recurrence represents a serious threat in the prognosis of CAV after surgery. Some of these recurrences, in particular liver metastases, are accessible for a curative treatment. This finding supports the usefulness of a close and long-term follow-up after surgery to improve survival of patients with CAV, especially in the group of patients with a good prognosis.

Key Words: pancreatoduodenectomy, ampulla of Vater, adenocarcinoma, follow-up, recurrence

Introduction

Carcinoma of the ampulla of Vater (CAV) is an uncommon tumor, which accounts for 7% of peri-pancreatic lesions [1]. Its prognosis is known to be better than pancreatic cancer after resection. Indeed, the 5-year survival median rate after resection has been reported to be around 45% (from 30 to >60%) in different series from the literature [2–31].

Some poor prognosis factors have been found, i.e. the large size of the tumor, lymph node metastases, vascular ingrowths and perineural microscopic invasion [3–5,12,20,23,24,28–31].

Recurrences have been poorly studied. Late recurrences have been reported but the median delay, the type and their curability are unknown. The aim of this study was to analyse the prognostic factors for survival and recurrence and to study specifically the recurrences and their management.

Patients and methods

Patients

From January 1985 to October 2003, all consecutive patients treated by pancreatoduodenectomy (PD) for CAV in the Department of Surgery of Caen were reviewed and analysed. There were 41 patients, 18 (44%) women and 23 (56%) men, with a mean age of 65 years (range 50–72). Symptoms at the time of diagnosis were jaundice (63%), right upper quadrant pain (34%), pancreatitis and angiocholitis. One patient presented with upper gastrointestinal bleeding; upper gastrointestinal endoscopy revealed a CAV (Table I).

Preoperative biopsies were available in 19 cases, 13 of which were positive for adenocarcinoma (68%). Ampullectomy had been performed previously for three patients. Two patients were diagnosed with

Table I. Baseline characteristics of patients ($n=41$).

Parameter	Value
Male, n (%)	18 (44%)
Age (SD)	65 (50–72)
T1	10 (24%)
T2	16 (39%)
T3	8 (20%)
T4	2 (5%)
Unknown	5
Differentiation	
Well differentiated	27 (66%)
Unknown	6 (15%)
Lymph node involvement	13 (32%)
Vascular invasion, n (%)	16 (39%)
Perineural invasion, n (%)	8 (19.5%)

adenoma 4 and 8 years before, respectively, and one with adenocarcinoma.

PD with lymphadenectomy was performed on all patients with the diagnosis or suspected diagnosis of CAV; 78% of patients had a pancreato-gastric anastomosis.

A single pathologist reviewed all specimens and patients' records were examined for characteristics of the initial tumor (Table I). The median size of the tumor was 2.3 cm. The tumors were well differentiated in 27 cases (65.8%). There was a mean of 11.6 nodes examined (1–40), with a median of <1 positive node (0–4). Four patients were treated postoperatively with radiation therapy associated with chemotherapy (40 Gy+5FU). Two tumors were well differentiated. Among those, there were two T2 lesions, one T3 and one T4. All of them had lymph node metastasis.

Methods

All patients were followed up every 3 months after surgery with regular monitoring of recurrence by ultrasonography or CT scan. The median follow-up was 48 months after the PD (range 2–161 months). Clinical and histological factors of survival and recurrence were analysed. The emphasis of the analysis was on the population of patients who had recurrences. We studied in detail the type of recurrence, the time between the initial surgery and the recurrence, and the treatment of this recurrence.

Statistical analysis

Survival following the day of surgery was evaluated by constructing Kaplan–Meier event curves in which all-cause death was considered as failure. Univariate analyses of factors potentially associated with survival and recurrences (age, sex, T stage, size of the lesion, perineural invasion, lymph node metastases, vascular involvement, differentiation) were based on the two-sided log-rank test. After checking the proportionality assumption and covariate colinearity, multivariate analysis of the time to death and time to recurrence

were performed with the Cox proportional hazards model to assess the independent effect of these variables. All analyses were conducted using SAS (version 8.2, SAS Institute Inc., Cary, NC, USA). p values <0.05 were considered to denote statistically significant differences. All tests were two-tailed.

Results

The 30 days postoperative and in-hospital mortality were 0% and 2%, respectively. Eighteen patients (43%) died during follow-up. The overall 1-year, 3-year and 5-year survival rates were 90.2%, 74.2% and 62.8%, respectively, with a 10-year survival rate of 34.6% (Figure 1).

On univariate analysis, age over 70, the existence of vascular ingrowths, perineural invasion and positive lymph nodes were statistically associated with survival ($p < 0.05$). (Figure 1). In our study, neither the size of the lesion (>2 cm) nor the differentiation of the tumor appeared to have a significant impact on survival.

Four independent factors (age >70 years, lymph node invasion, perineural infiltration and recurrence) had a significant impact on survival ($p < 0.05$) (Figure 2).

Recurrence occurred in 11 cases (26.8%), with a median time of 24.5 months after PD (range 6–67 months). Recurrence occurred as follows: seven patients experienced peritoneal metastases with in one case liver involvement, two patients had solitary liver metastasis, one had bilateral hepatic metastasis and one patient had a biliary recurrence.

On multivariate analysis, three independent factors were predictive of recurrence: lymph node metastasis (HR 5.3, $p=0.02$), perineural invasion (HR 5.3, $p=0.02$) and tumor differentiation (HR 0.2, $p=0.05$).

Seven patients with peritoneal metastases had recurrences 24.8 months after initial surgery. There were two T1 lesions, two T2 lesions, two T3 lesions and one T4. Six of the seven patients had well differentiated tumors. All had positive lymph nodes on final pathology; 71% had perineural invasion, whereas only 43% had vascular ingrowths. Three of

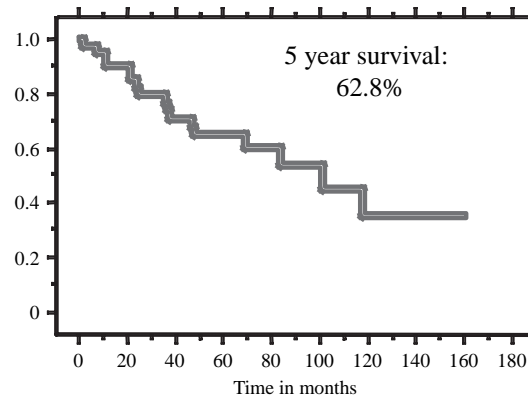


Figure 1. Overall survival.

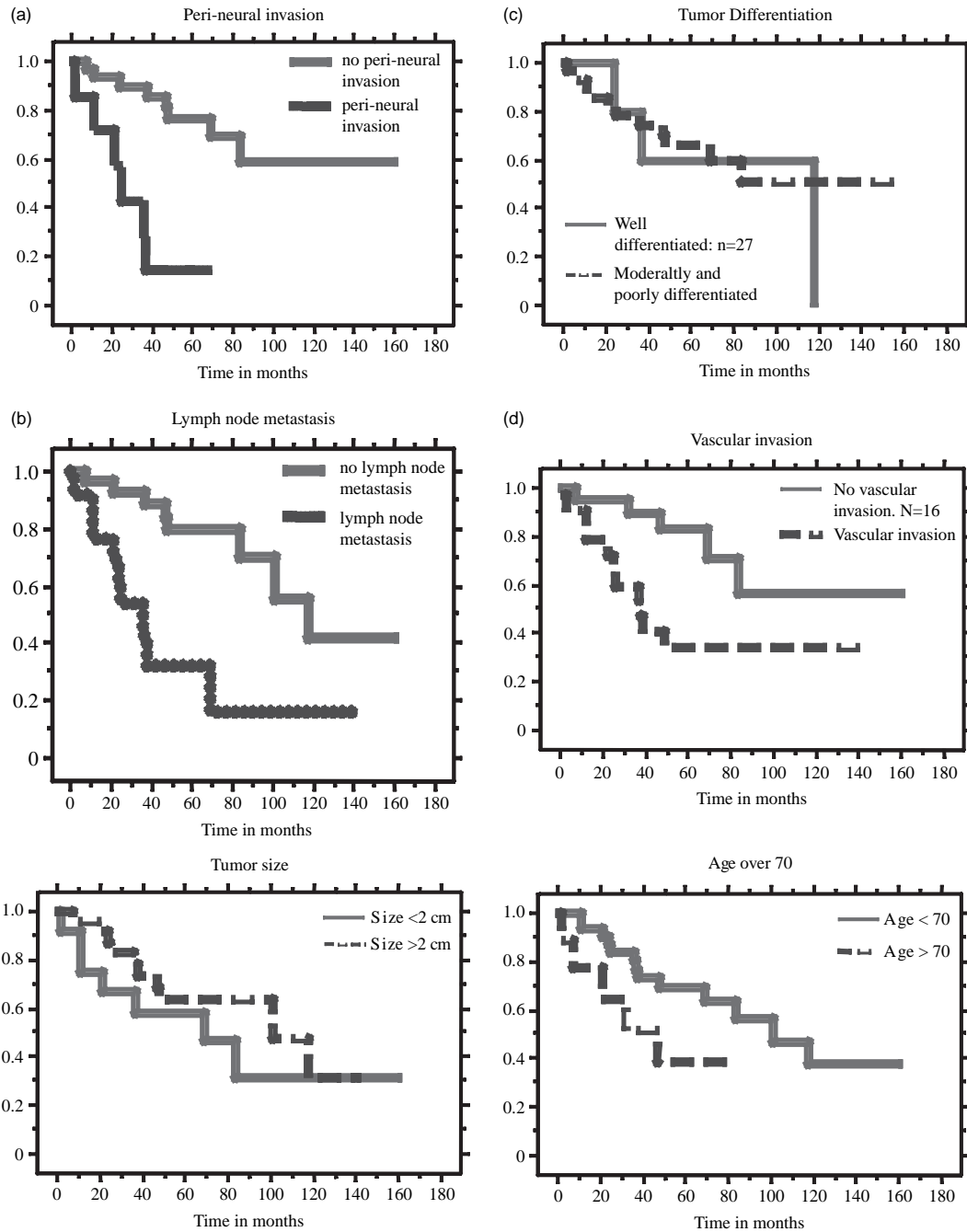


Figure 2. Kaplan Meier survival curves according to different baseline factors.

these seven patients had a postoperative treatment based on radiation and chemotherapy. These patients were N+ and experienced peritoneal metastases 6, 18 and 26 months after the PD. Two patients were treated for recurrence with radiation therapy and chemotherapy, one of whom had already had a postoperative treatment.

Two patients had isolated liver metastasis. There were two T2 lesions with no positive lymph nodes or vascular ingrowth. One of them had perineural invasion. None of these patients had received postoperative treatment. Liver metastasis was diagnosed during systematic follow-up, at 10 and 11 months after surgery. These lesions were both treated aggressively, with R0 minor liver resection. Both of these two

patients are alive and tumor-free 39 and 45 months after treatment of recurrence. One patient experienced a biliary recurrence 67 months after surgical resection of a T1 CAV. He was treated by segmentectomy 4 with biliary reconstruction on a Roux-en-Y jejunal loop. Then 33 months later he experienced an angiocholitis, with an abscess on the right lobe of the liver for which he was re-operated (right hepatectomy). On final pathology, recurrences on liver, jejunal loop, portal vein and retroportal lymph nodes were observed. He died 2 months after surgery. The only patient who recurred with bilobar liver metastases was treated by intra-arterial hepatic chemo-embolization, at the beginning of our experience. He died early after his first treatment.

Table II. Factors predictive of survival: review of the literature.

Authors (Ref. no.)	Year(s)	n (CAV)	Periampullary tumors included	Mortality rate	5-year survival	Prognosis factors									
						N	T	R0	VI	PNI	Diff	Others			
Seller & Machacek [2]	1993	18	Y		40%										
Shutze et al. [3]	1953–1988	24	N	12.50%	61%	+									
Chan et al. [4]	1960–1991	29	Y		42% (disease-free)			+		+					Chemotherapy
Monson et al. [5]	1965–1989	104	N	6%	34%	+	+		+						
Su et al. [6]	1965–1995	132	N	15.20%	37.50%	+	+								>75 years, ht >30%, urea <20 mg/dl
Talamini et al. [7]	1969–1996	106	N	4%	38.00%	+									Perioperative transfusion
Yeo et al. [8]	1970–1992	46	Y		39%										
Chareton et al. [9]	1970–1992	63	N		40%										
Dorandeu et al. [10]	1970–1992	45	N		44%	+	+								
Sperti et al. [11]	1971–1990	36	N	3%	56%	+	+								+
Klempnaueur et al. [12]	1971–1995	85	N	9.60%	38.20%	+	+								+
Sielezneff et al. [13]	1971–1995	39	N	10%	35%	+	+								+
Kayahara et al. [14]	1974–1994	36	N	8%	56%										
Shirai et al. [15]	1975–1991	56	N	2.50%	45%	+									
Allema et al. [16]	1975–1993	982		12%	35%										
Menon et al. [17]	1975–1997	13	N	0%	38%	+									
Andersen et al. [18]	1976–1991	25	Y		34%	+									
Willett et al. [19]	1981–1990	29	N		55%										
Beger et al. [20]	1982–1997	126	Y		52% if R0	+		+	+						
Matory et al. [21]	1983–1990	69	N		43%										Resectability
Howe et al. [22]	1983–1995	101	N	5%	44%	+		+							
Tanaka et al. [23]	1983–1999	16	N	0%	50.50%	+			+	+					
Allema et al. [24]	1984–1992	62	N	6%	50%			+							
Bottger et al. [25]	1985–1994	31	N		63%	+									
Stephens et al. [26]	1985–1995	28	Y		41%	+									
Kingsnorth [27]	1987–1995	29	Y		34%										
Lee et al. [28]	1988–1997	39	N	5%	55% (3-year survival)	+									
Duffy et al. [29]	1988–2001	55	N	0	67.70%						+				
de Castro et al. [30]	1992–2002	145	N	5%	37%	+		+			+				
Brown et al. [31]	1991–2004	51	N	2%	58%	+									
Hansel et al. [32]			N			+	+		+						CDX

N, lymph node metastases; T, tumor stage; R0, curative resection; VI, vascular invasion; PNI, perineural invasion; Diff, tumor differentiation; CDX, caudal type homeodomain transcription factors.

Discussion

Our study confirms the good results of curative resection for CAV, possible in all cases in our series, with a low postoperative mortality rate. Series in the literature vary 13 to more than 100 patients, reviewed on at least 10 year. Our serie is monocentric, reviewing 41 patients operated on a 18 year period of time.

The 5-year survival rates reported in different series in the literature vary from 35% to 67.7% [2–32] (Table II). In the first period of time, from 1975 until 1993, the 5-year survival rate reported among 932 patients was 35% [16]. An increase of this survival was observed during the following 20 years, with a 5-year survival rate of nearly 45% (34–67.7%). With a 5-year survival rate of 62.8%, we report one of the four top survival rates of >60% [25,29] (Table II).

Many different prognosis factors have been reported in the literature. The most common one is lymph node metastasis. Indeed many series report a better survival when no lymph node metastasis was found [3,4,8,13,17,30]. The other most common factors found in literature were resection margin status [24], tumor differentiation [6,13,15], T stage [5,6,12,13,16] and perineural invasion [23,29,30]. The existence of vascular invasion was observed less frequently [5,23] (Table II).

Our study points out the same prognosis factors but multivariate analysis emphasizes the impact of perineural invasion on all-cause mortality. Among patients who experienced a curable recurrence, all were N–, but two-thirds had perineural invasion. If we focus on modalities of tumor relapse, several characteristics can be outlined, as described below.

First, recurrence after PD for CAV is a frequent event, occurring in about 50% of patients [23,28,33]. Recurrence is linked to the tumor characteristics and especially to the T and N stages. Indeed, de Castro et al. reported an increased rate of recurrence varying from 32% in T1–T3N0 stages and 100% for T4N+ lesions [33]. Tumor differentiation is also predictive of recurrence [5,6,12,13]. An interesting aspect of our patients who had recurrences was that they had predictive factors of favorable outcomes on pathology (i.e. no lymph node metastasis).

Second, the site of first recurrence appears to be mainly in the liver, the tumor bed and the peritoneum [11,33]. Lung and bilateral ovarian metastases were among other sites reported [11,34]. In contrast, we report the first case of metastatic biliary ingrowths, appearing 67 months after resection, probably because of biliary dysplasia associated with the ampulloma. But our experience suggests a low rate of solitary liver metastasis (5%).

Third, the delay of recurrence is an important fact concerning the need for a long follow-up. Indeed, after PD, patients are usually followed for 5 years with systematic ultrasound examination. Most recurrences occur in the first 3 years [23,31], with 25% in the first

6 months after surgery according to de Castro et al. [33]. But late recurrences have also been reported (42–114 months) [11,33]. In our series we found only 26.8% of patients who had recurrences with a mean time to recurrence of 27.6 months. The latest recurrence occurred 67 months after PD.

Consequently, even if this tumor seems to have a good prognosis in terms of survival, a close and long-term follow-up in CAV should be recommended, to detect treatable recurrences at an early stage.

As regards the curative treatment of these recurrences, very few data are available in current literature. Liver metastases are the most frequently curatively treated. Fujii et al. in 1999 reported two liver resections for CAV metastasis [35]. Both patients were diagnosed with unilobar liver metastases 22 and 23 months after PD. They were operated on (extended left hepatectomy and right hepatectomy) but experienced an early recurrence. In 2002 Yoshida et al. reported one case of liver metastasis 19 months after PD for a T2N1 CAV [36]. This 51-year-old woman was treated with preoperative and postoperative chemotherapy and was still alive with no sign of recurrence 18 months after surgery. In our series, we report two patients (5%) who recurred with unique liver tumors, 10 months after PD. They were operated on and are still alive with no sign of recurrence 45 and 39 months after liver surgery.

The treatment of such liver recurrences definitely leads to an increase in survival, in contrast with a short survival of 4.7 months after the diagnosis of metastasis [33]. Local bed recurrences are often associated with peritoneal metastases, and no curative treatment is available.

In our series, we experienced one biliary tumor budding 67 months after PD, which was successfully treated with liver and bile duct resection, allowing a long-term survival.

To conclude, our experience shows that treatment of recurrence is possible in some selected cases, especially for solitary liver metastasis and seems to allow a long-lasting survival. We suggest a careful and long-term follow-up even in patients with good prognosis factors. As these recurrences are mostly asymptomatic, systematic monitoring by ultrasonography or CT scan is advisable, especially in the first 3 years. An aggressive treatment of such recurrences is also advisable.

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