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Tumors of ampulla of Vater: A case series and review of chemotherapy options

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Abstract

Carcinomas of the Ampulla of Vater are rare tumors, accounting for 0.2% of gastrointestinal cancers. Compared with other biliary tract neoplasms, these tumors have a relatively favorable prognosis after surgical resection. Based on their epithelium of origin, two subtypes of ampullary carcinoma have been recently distinguished: intestinal and pancreatobiliary. This study evaluates histopathological features and outcomes of ampullary carcinoma and to compares the survival of these tumors to that of other biliary tract tumors. The chemotherapeutic options available for ampullary cancer are also reviewed. We analyzed data from 20 consecutive patients with ampullary carcinomas and 26 patients with other biliary tract carcinomas, observed in our Institution. Statistical analysis was performed by using either Fisher's exact test or χ^2 test for categorical variables. Median time of survival was calculated and compared using the Log-Rank test. Similar distribu-

tion of demographic characteristics and stage between ampullary and other biliary tract cancers was observed. Patients with ampullary cancer underwent surgery more frequently than other biliary cancers while chemotherapy and radiotherapy were used equally. In accordance with the literature, a longer median survival was observed in the group of ampullary carcinomas.

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Key words: Ampullary carcinoma; Chemotherapy; Radiotherapy; Biliary tract cancer

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INTRODUCTION

In clinical trials concerning chemotherapy treatments, tumors of the ampulla of Vater are usually included in the group of pancreato-biliary tumors, although some data recognize their histological and clinical peculiarities. Only a few studies have focused on this specific group of tumors and the available case series are generally small. This study aimed to describe our own series of ampullary cancers, including the histopathological features and outcome. Moreover the survival of these patients was compared with that of a group of other biliary tract tumors. A review of chemotherapy options available for ampullary cancer was also carried out.

TUMORS OF THE AMPULLA OF VATER: AN OVERVIEW

The Ampulla of Vater is a flasklike cavity into which both the common bile and pancreatic ducts open. However, in 42% of patients, the ampulla is the termination of common bile duct alone and the pancreatic duct enters the duodenum separately, adjacent to the ampulla. The ampulla is 1.5 cm long or less, traverses the duodenal wall, opens into the duodenal lumen through (major) duodenal papilla (papilla of Vater) and is surrounded by the pancreas and duodenum. The area within 2 cm of the ampulla is called periampullary region. Periampullary cancers account for 5% of all gastrointestinal cancers, whilst cancer of the ampulla is rare (0.2% of the cases)^[1,2].

Most ampullary tumors are adenocarcinomas, but are occasionally papillary, adenosquamous or mucinous. Recent studies have reviewed histopathological findings of such tumors, identifying two distinct histological types of adenocarcinoma based on their epithelium of origin: intestinal and pancreatobiliary^[3-6]. Intestinal ampullary adenocarcinomas originate from the intestinal epithelium overlying the ampulla whereas pancreatobiliary ampullary carcinomas originate from the epithelium of the distal common bile duct and distal pancreatic duct. The intestinal subtype usually expresses cytocheratin (CK)20 and caudal homeobox gene transcription factor 2 (CDX2)^[7,8], whereas biliopancreatic differentiation is generally characterized by a positive immunostaining for apomucins (MUC 1, MUC5a), CK7^[4], CK17 and negativity for CDX2^[7,8]. Moreover, with MUC 2 mostly positive in intestinal subtype, positivity for MUC2 and CDX2 is used to exclude pancreatobiliary origin whereas positivity for MUC1 and CK17 is used to exclude intestinal origin^[8]. The study of microsatellite instability (MSI) pattern in ampullary tumours showed a significant association between high-MSI and intestinal mucinous differentiation^[9]. A high proportion of ampullary carcinomas have both COX-2 and vascular endothelial growth factor highly expressed^[10].

Curative surgery is feasible in about 50% of ampullary cancer whilst a rate of up to 10% is reported for pancreatic cancer^[11,12]. Due to the peculiar anatomy of the Ampulla of Vater, the early onset of cancer symptoms makes ampullary tumors more likely to be resected than other pancreatobiliary cancers^[2]. Following ampullary carcinoma resection, survival appears to be intermediate between duodenal and pancreatic or distal bile duct cancer^[2,13,14]. In more recent studies, a 5-year survival rate ranging from 33% to 68% has been reported in ampullary cancer^[15-24]. Besides classical prognostic parameters, such as lymph node involvement^[11,20,21,25], depth of infiltration^[11,21,25,26], and lymphovascular invasion^[26,27], tumor type (intestinal *vs* pancreatobiliary) plays a distinct role in survival in ampullary cancer^[26,27]. Notably, intestinal differentiation confers a statistically significant survival advantage both in periampullary and in ampullary carcinoma, making the survival rate of ampullary cancer simi-

lar to that of duodenal cancer^[27]. Conversely, the survival rate of ampullary cancer with pancreatobiliary differentiation appears to be comparable to that of pancreatic cancer^[26,27].

The assessment and staging of ampullary neoplasms is based on several diagnostic modalities, including extracorporeal ultrasonography (US), computed tomography (CT), magnetic resonance cholangiopancreatography, esophagogastro-duodenoscopy, endoscopic US (EUS), endoscopic-retrograde cholangiopancreatography, intra-ductal US (IDUS) and biopsy. Detection of ampullary carcinoma and both tumor extension and metastatic lymph nodes is better with EUS than US and CT scan^[28] and equal to magnetic resonance imaging (MRI)^[29]. Transpapillary IDUS demonstrates good accuracy in the detection of tumor infiltration of ampullary cancer^[30], whereas CT and MRI are recommended for the detection of distant metastases.

Pancreaticoduodenectomy (Whipple procedure) is regarded as the standard treatment for ampullary cancers whereas endoscopic ampullectomy is typically reserved for benign ampullary lesions. Definitive consensus guidelines for the use of adjuvant or neoadjuvant chemotherapy and radiation therapy in ampullary cancer are lacking and, in general, treatment is individualized and/or based on institutional protocols. In locally unresectable or metastatic cancer, both chemoradiotherapy and chemotherapy can be applied although the lack of randomized controlled trials prevents the choice of any treatment as standard. Fluoropyrimidines, cisplatin, and gemcitabine are the most commonly used drugs in ampullary carcinoma, but the best combination and protocol remain to be identified.

CASE SERIES

Medical records of patients diagnosed with ampullary and other biliary tract tumors, observed at our Institution from 2005 to 2010 were reviewed. In particular, we analyzed demographic characteristics, tumor histology, UICC stage, treatments employed and survival time for consecutive ampullary and biliary tract carcinoma patients. According to the Kimura classification^[6], ampullary cancers were divided in intestinal and pancreatobiliary, depending on their histological differentiation. To compare characteristics, Student's T test, Fisher's exact test or χ^2 tests for categorical variables were used, as appropriate. Median time of survival was calculated and compared using the Log-Rank test.

Overall, we identified 20 patients with ampullary and 26 patients with other biliary tract carcinomas (gallbladder: 11 cases, intrahepatic bile duct: 10, extrahepatic bile duct: 5). The median age at diagnosis was 64 years (range: 33-83 years) and 68 years (range 55-80 years), respectively. Other demographic characteristics, histological features, stage, treatment received and outcome of patients with ampullary cancer are shown in Table 1. In detail, 11 patients (55%) were classified as intestinal type, 8 (40%) as pancreatobiliary and 1 as neuroendocrine. Nineteen (95%)

Table 1 Demographics, histological features, stage, treatment received and outcome of 20 cases of ampullary carcinoma

No.	Age (yr)	Gender	PS	Tumor subtype	Grade	Stage	Adjuvant therapy	Site of failure	First Line Therapy	Response	TTP (mo)	Status	OS (mo)
1	77	F	1	Intestinal	G2	LD	Op + 5FU-CCRT	NA	NA	NA	NA	DOD	14
2	63	M	0	Intestinal	G3	LD	Op + FOLFOX	----	----	----	----	NED	17
3	45	M	0	Pancreatobiliary	G2	LD	Op + 5FU-CCRT	NA	NA	NA	NA	DOD	48
4	70	M	1	Intestinal	G2	LD	Op	Lymphnodes	CDDP-Gem	PD	11	DOD	20
5	73	F	0	Intestinal	G1	LD	Op	----	----	----	----	NED	57
6	60	M	1	Intestinal	G2	LD	Op + 5FU-FA	----	----	----	----	DOO	36
7	73	M	0	Pancreatobiliary	----	ED	----	Peritoneal	Gem-Cap	PD	3	DOD	4
8	79	F	2	Pancreatobiliary	----	LD	Op + Cap-CCRT	----	----	----	----	NED	22
9	68	F	0	Pancreatobiliary	G2	LD	Op	----	----	----	----	NED	219
10	83	F	0	Intestinal	G2	LD	Op	----	----	----	----	NED	41
11	65	M	2	Neuroendocrine	G4	LD	Op + CDDP-VP16	Liver	Topotecan	PD	2	DOD	10
12	68	M	0	Intestinal	G3	LD	Op + FOLFOX	----	----	----	----	NED	22
13	48	F	1	Intestinal	G3	LD	Op + 5FU-CCRT	Lung	Gem-Oxa	PD	2	DOD	23
14	49	F	1	Intestinal	G1	LD	Op + Cap-CCRT	----	----	----	----	NED	24
15	71	F	1	Pancreatobiliary	G1	LD	Op	----	----	----	----	NED	44
16	61	M	0	Pancreatobiliary	G1	LD	Op + Gem + RT	Multiple	5FU	PD	12	DOD	16
17	65	F	2	Intestinal	G3	LD	Op + FOLFOX	Liver	Gem	PD	14	DOD	19
18	79	M	2	Pancreatobiliary	G3	LD	Op	Liver	NA	PD	4	LOF	----
19	45	F	0	Pancreatobiliary	G3	LD	Op + 5FU-CCRT	Lung	Gem-Oxa	PD	4	DOD	10
20	33	F	0	Intestinal	G1	LD	Op + Cap-CCRT	----	----	----	----	NED	30

PS: ECOG Performance status; TTP: Time to progression; LD: Limited disease; ED: Extended disease; Op: Operation; CCRT: Concurrent chemoradiotherapy; 5FU: 5-fluorouracil; FA: Folinic acid; OXA: Oxaliplatin; FOLFOX: 5FU + FA + OXA; Cap: Capecitabine; CDDP: Cisplatin; VP16: Etoposide; Gem: Gemcitabine; NA: Not applicable; PD: Progressive disease; DOD: Died of disease; NED: No evidence of disease; DOO: Died of other cause; LOF: Lost of follow-up; OS: Overall survival.

patients underwent a surgical resection and 13 (68.4%) of these also received an adjuvant therapy, including chemotherapy alone in 5 cases and a combined chemo-radiotherapy (CCRT) in the remaining patients. Ten (50%) patients experienced disease progression. In most of these cases a first-line chemotherapy was administered [gemcitabine-oxaliplatin: 2 cases, gemcitabine-cisplatin: 1, gemcitabine-capecitabine: 1, gemcitabine: 1, 5-fluorouracil (5FU): 1], whilst the neuroendocrine tumor patient received topotecan. Median survival was 22 mo (range: 4-57 mo). Twelve (46.1%) of the 26 patients with other biliary tract tumors underwent surgical resection, and 8 (66.7%) of these also received an adjuvant therapy, comprising chemotherapy alone in 3 cases and a CCRT in the remaining patients. Seventeen (65.4%) patients experienced disease progression, and 12 of these patients received first-line chemotherapy (gemcitabine-oxaliplatin: 4 cases, gemcitabine-5FU: 1, gemcitabine: 1, Fluoropirimidin-based regimen: 6). Median survival was 11.5 mo (range: 1-60 mo). As shown in Table 2, surgical resection was more frequently feasible in patients with ampullary cancers (95%) than in those with biliary cancers at other sites (46.1%), the difference being statistically significant ($P < 0.05$). Overall, patients with ampullary carcinoma showed a significantly higher median survival than those patients with other biliary tumors (22 mo *vs* 11.5 mo, $P < 0.05$).

REVIEW OF THE LITERATURE

Early disease and adjuvant treatment

Postoperative (adjuvant) treatments, such as chemotherapy and/or radiotherapy, can be used to reduce the loco-

Table 2 Demographics, histological features, stage, treatment received and outcome of patients affected with ampullary or other biliary tract tumors *n* (%)

	Ampullary tumors (<i>n</i> = 20)	Other biliary tumors (<i>n</i> = 26)	<i>P</i> -value
Gender			
Male	9 (45)	10 (38.5)	NS
Female	11 (55)	16 (61.5)	
Tumor subtype			
Intestinal	11 (55)		NS
Pancreato-biliary	8 (40)		
Others	1 (5)		
Grade			
1-2	11 (55)	7 (66.7)	NS
3-4	7 (45)	5 (33.3)	
UICC Stage			
I	4 (20)	4 (15.4)	NS
II	10 (50)	10 (38.5)	
III	4 (20)	3 (11.5)	
IV	2 (10)	9 (34.6)	
Surgery	19 (95)	12 (46.1)	< 0.05
Chemotherapy	9 (45)	14 (53.8)	NS
Chemo-radiotherapy	8 (40)	7 (26.9)	NS

NS: Not significant.

regional or distant relapse and to achieve an improvement in the survival time. Only a few retrospective studies have focused on the adjuvant treatment in ampullary cancer, whilst ampullary tumors more often constitute a subgroup of pancreato-biliary tumors included in adjuvant clinical trials. Radiotherapy alone has been tested in patients with extrahepatic bile duct carcinoma in only a few studies, and with conflicting results^[31-33].

Table 3 Studies on adjuvant chemo-radiotherapy

	<i>n</i>	Study design	Treatment group	Control group	Treatment benefit	Author
Pancreatic + periampullary	207	RCT (EORTC)	CCRT	Observation	No	Klinkenbijl <i>et al</i> ^[36] 1999
Ampullary	104	Retrospective	CCRT	Observation	No	Sikora <i>et al</i> ^[37] 2005
Ampullary	125	Retrospective	CCRT	Observation	Yes (node+)	Bhatia <i>et al</i> ^[38] 2006
Pancreatic + periampullary	218	RCT	CCRT	Observation	No	Smeenk <i>et al</i> ^[39] 2007
Ampullary	96	Retrospective	CCRT	Observation	No	Krishnan <i>et al</i> ^[40] 2008
Pancreatic + periampullary	120	RCT	CAI + RT	Observation	Yes	Morak <i>et al</i> ^[41] 2008
Ampullary	118	Retrospective	CCRT	Observation	Yes	Kim <i>et al</i> ^[42] 2009
Ampullary	111	Retrospective	CCRT	Observation	No	Zhou <i>et al</i> ^[43] 2009
Extra hepatic biliary cancer	120	Retrospective	CCRT + CT	CCRT	Yes	Lim <i>et al</i> ^[44] 2009
Ampullary	186	Retrospective	CCRT	Observation	Yes	Narang <i>et al</i> ^[45] 2011

RCT: Randomized controlled trial; CCRT: Combined chemio-radiotherapy; CAI: Celiac axis infusion (intra-arterial chemotherapy); RT: Radiotherapy; CT: Chemotherapy.

Few studies are available on the use of intraoperative radiation therapy^[34,35], with data generally drawn from studies on adjuvant CCRT (Table 3)^[36-45]. Unfortunately, the benefit achieved following postoperative chemo-radiation in patients with pancreatic, periampullary and ampullary cancer observed in some studies^[38,40,42,45] was not confirmed in others, including two randomized studies^[37,39,41,43]. In the EORTC 40891 study, 218 patients with T1-2 N0-1 aM0 pancreatic and T1-3N0-1aM0 periampullary cancer were randomized to either chemoradiotherapy regimen (5-FU given as a continuous infusion during radiotherapy) or observation^[39]. The overall survival (OS) did not significantly differ between the two treatment groups, although the 10-year OS was 29% and 8% in the periampullary and pancreatic cancer, respectively. In another randomized study, 120 patients with pancreatic or periampullary cancer received either adjuvant intra-arterial chemotherapy (mitoxantrone, 5-FU, leucovorin, and cisplatin) combined with radiotherapy or no adjuvant treatment^[41]. Disappointingly, no significant survival advantage was observed in the treatment group although CCRT produced a significant reduction in the appearance of liver metastases in periampullary tumors. One study evaluated the role of an additive chemotherapy following CCRT in patients with histologically confirmed, non-metastatic adenocarcinoma of extrahepatic biliary tract excluding gallbladder and periampullary cancer^[43]. Both 3-year disease-free and OS were increased by the use of chemotherapy after a CCRT, when compared to CCRT alone (45.2% *vs* 26.6% and 62.6% *vs* 30.8%, respectively, $P < 0.05$).

One phase III multicenter randomized trial tested the role of adjuvant chemotherapy in 508 pancreatico-biliary carcinoma^[46]. The study recruited patients with resected pancreatic ($n = 173$), bile duct ($n = 139$), gallbladder ($n = 140$), or ampulla of Vater ($n = 56$) carcinomas in two arms: adjuvant therapy with mitomycin C and 5-FU (MF arm) and surgery alone (control arm). A significantly higher 5-year survival rate in gallbladder carcinoma patients was detected in the MF group as compared to the control group (26% *vs* 14.4%, $P < 0.05$). Conversely, no survival advantage was reported between patients

with pancreatic, bile duct, or ampullary carcinomas. The primary role of the adjuvant chemotherapy in the treatment of pancreatic cancer firstly emerged in the ESPAC study^[47], and more recently confirmed by the CONKO 001 study^[48,49]. The former, a 2×2 factorial design study including more than 280 patients, demonstrated a survival benefit in patients receiving postoperative 5-FU-based chemotherapy and a detrimental effect of postoperative CCRT. The latter detected, in the group of patients receiving postoperative gemcitabine, a statistically significant benefit, both in the disease-free and in OS. The efficacy of a gemcitabine-based as compared to a 5FU-based adjuvant treatment was also emphasized by another trial, in which chemotherapy for 3 wk prior and for 12 wk after CCRT was administered^[50]. In agreement with these data, adjuvant gemcitabine-based chemotherapy was found to be a significant independent predictor of a favourable prognosis in patients with hilar cholangiocarcinoma^[51]. In the ESPAC-3 study, 304 patients with ampullary cancer were randomized to adjuvant chemotherapy ($n = 199$; 101 5FU, 98 Gemcitabine) and 105 to observation^[52]. Compared to the control group, a survival benefit was observed in patients, with a R0 resection treated with adjuvant chemotherapy ($P = 0.057$).

Locally advanced and metastatic disease

Surgery represents the main therapeutic approach for ampullary cancer, whilst unresectable tumors can be treated with either radiotherapy or chemotherapy. However, due to the limited data available, the role of radiation therapy remains to be defined. To achieve better results, external beam radiation therapy has been combined with intraluminal brachytherapy and/or chemotherapy^[53]. Metastatic/advanced ampullary adenocarcinoma has a poor prognosis, with an OS rate at 2 years ranging from 5% to 10%^[54]. There is no standard chemotherapeutic regimen for metastatic disease. The role of chemotherapy in advanced biliary cancer was assessed in a study in which palliative chemotherapy achieved survival advantage and improved quality of life when compared with best supportive care^[55]. A pooled analysis of 104 clinical trials, comprising 2810 patients, showed that a single-agent

antimetabolite (5FU or gemcitabine) is better than any other single drug, as well as that a combined schedule of antimetabolites plus platinum salts is more effective than a single agent or any other doublet^[56], the most promising combinations being gemcitabine plus cisplatin^[57], and gemcitabine plus oxaliplatin^[58]. Several clinical trials have reported a wide range of response rate (RR) and OS time, using a regimen of 5-FU, cisplatin and epirubicin (RR: 10%-40%; median OS: 5-11 mo) to treat biliary tract neoplasms^[59-62]. The combination of 5-FU, doxorubicin and mitomycin (FAM regimen), in 38 patients with advanced small bowel adenocarcinoma and ampullary adenocarcinoma, demonstrated a RR of 18% and a median OS of 8 mo^[63]. A combination regimen comprising capecitabine and oxaliplatin, in 30 patients with advanced small bowel adenocarcinoma and ampullary adenocarcinoma ($n = 12$), achieved a RR of 33% in ampullary tumors, whilst the median TTP and OS of all patients were 11.3 and 20.4 mo, respectively^[64]. Another phase II study evaluated outcomes in 29 patients with advanced ampullary adenocarcinoma using 3 different schedules with cisplatin and 5-FU or capecitabine or gemcitabine^[65]. Overall, a RR of 27.5% and median survival of 12.5 mo, with no significant differences among different regimens used, were observed.

Combination of gemcitabine with either oxaliplatin or capecitabine achieved a RR of about 30% and a median PFS from 5.7 to 7 mo. The GERCOR study investigated gemcitabine plus oxaliplatin (GEMOX regimen) in a cohort of 56 patients with advanced biliary tract adenocarcinoma, including 3 cases of ampullary adenocarcinoma^[66]. Patients were divided in 2 subgroups: group A ($n = 33$) included patients with eligible criteria for phase II studies and group B ($n = 23$) included patients who would normally be excluded from such studies (PS > 2 and/or bilirubin > 2.5 \times normal and/or prior chemotherapy). In group A, there was an objective response in 36% of cases, with median PFS of 5.7 mo and OS of 15.4 mo, whilst in group B objective response was 22%, PFS 3.9 mo, and OS 7.6 mo. A gemcitabine plus capecitabine schedule was tested in 45 patients with advanced biliary cancer and no prior chemotherapy^[67]. The overall objective RR and stable disease were 31% and 42%, respectively, the median PFS was 7 mo and OS was 14 mo. A recent study was conducted on 37 patients with advanced biliary tract adenocarcinoma (19% patients had an ampullary adenocarcinoma) using a 4-drug regimen (PEFG: Cisplatin 40 mg/mq + Epirubicin 40 mg/mq on Day 1; Gemcitabine 600 mg/mq on Day 1 and 8; 5-FU 200 mg/mq daily as continuous infusion)^[68]. Overall, 43% of patients achieved a partial response, with median survival of 12.1 mo, and a 1-year OS rate of 52%. In this study, ampullary cancer was significantly more responsive to chemotherapy than biliary tract ($P < 0.05$) and gallbladder cancer ($P = 0.057$), although the sample size of each subgroup was too small to allow reliable conclusions. A recent randomized phase III study assigned 410 patients with locally advanced or metastatic biliary tract cancer to receive cisplatin (25 mg/mq D1)

+ gemcitabine (1000 mg/mq D1 and 8) or gemcitabine alone^[69]. There were 206 patients in the gemcitabine-group (ampullary: 11 cases, 5.3%) and 204 patients in the cisplatin + gemcitabine-group (ampullary: 9 cases, 4.4%). The median PFS was 8 mo in the cisplatin+gemcitabine-group and 5 mo in the gemcitabine-group. The median OS was 11.7 mo and 8.1 mo in the doublet-regimen and in the gemcitabine-group, respectively, indicating a significant survival advantage. This UK study defined a new standard of care and demonstrated that it is now possible to perform large scale studies in advanced biliary cancer.

Targeted therapies represent a new, interesting chapter in cancer treatment. To date, there are no consistent data concerning biliary tree tumors and antiangiogenic drugs and only a few studies concerning anti-epidermal growth factor receptor (EGFR) drugs. Results of one phase II study, evaluating GEMOX plus Cetuximab in 30 cholangiocarcinoma patients, showed a surprisingly high RR (63.3%) along with good tolerability^[70]. The French BINGO trial, a multicenter randomized phase II study, tested the efficacy of GEMOX alone or in combination with bi-weekly Cetuximab in the first-line treatment of advanced biliary cancer^[71]. Overall 101 patients were divided in two treatment groups: arm A received GEMOX (Gemcitabine 1000 mg/mq D1 + Oxaliplatin 100 mg/mq D2) and arm B received GEMOX plus Cetuximab (500 mg/mq bi-weekly). The preliminary results (4-mo at interim analysis) from 36 patients showed a PFS of 44% in arm A and 61% in arm B, indicating a significant activity of Cetuximab. Since EGFR overexpression strongly correlates with tumor progression in biliary cancer^[72], the use of anti EGFR seems to be a promising therapeutic option. However, well conducted prospective clinical trials are needed to understand the role of such drugs in ampullary cancer.

CONCLUSION

What did we learn from our study and what suggestions come from the literature? There is no conclusive data that confirm the usefulness of adjuvant radiotherapy or CCRT in biliary tract cancer whereas favorable results support the use of adjuvant chemotherapy. An acceptable standard of chemotherapy in a setting of advanced ampullary adenocarcinoma may be the cisplatin-gemcitabine regimen. However, the small sample size of patients with ampullary carcinoma recruited in the ABC 02 study, and lack of other randomized trials, make the optimal treatment for these patients still debatable. Histopathology, molecular features and clinical outcome clearly identify two distinct types of ampullary cancer, and their differences should be taken into account both in selecting medical treatments and in planning clinical trials.

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