

Metachronous Ampulla of Vater Carcinoma after Curative-Intent Surgery for Klatskin Tumor

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Rezumat

Carcinom metacron de ampulă Vater după rezecție de tumoră Klatskin

Rezecția reprezintă singura șansă de supraviețuire la distanță în cazul pacienților diagnosticați cu colangiocarcinom hilar (tumora Klatskin). Totuși, la majoritatea pacienților rezecați boala recidivează. Apariția unui al doilea cancer, metacron, după chirurgia cu vază curativă a unei tumori Klatskin reprezintă o patologie de excepție, iar atitudinea terapeutică în aceste cazuri nu este codificată. Este prezentat un pacient de 32 de ani cu rezecție de cale biliară extrahepatică, hemi-hepatectomie stângă și limfadenectomie loco-regională pentru o tumoră Klatskin tip IIIB Bismuth-Corlette, pacient căruia, ulterior, la 6 ani distanță, i s-a practicat o duodenopancreatectomie cefalică pentru un carcinom metacron de ampulă Vater. Atitudinea terapeutică și evoluția postoperatorie a pacientului sunt discutate împreună cu o evaluare a cazurilor comunicate anterior în literatura de specialitate. În concluzie, apariția unui carcinom periampular metacron după rezecția unei tumori Klatskin trebuie diferențiată de recidiva loco-regională. Majoritatea pacienților cu recidivă tumorală pot beneficia doar de tratament chimio și/ sau radioterapic, în timp ce la cea mai mare parte dintre pacienții cu neoplasm metacron o a doua intervenție cu vază curativă de tip duodenopancreatectomie cefalică este fezabilă și asociată cu rezultate bune pe termen lung.

Cuvinte cheie: colangiocarcinom hilar, neoplasm metacron, carcinom de ampulă Vater, duodenopancreatectomie cefalică

Abstract

Resection represents the single hope for long-term survival in a patient diagnosed with a hilar cholangiocarcinoma (Klatskin tumor). However, the largest part of these patients develops a recurrent disease. Second metachronous periampullary cancers after a curative-intent surgery for a Klatskin tumor represent an exceptional pathology, and the management of these patients was poorly documented. Hereby, it is presented a 32-year-old patient with bile duct resection, left hemi-hepatectomy and loco-regional lymph nodes dissection, for a type IIIB Bismuth-Corlette Klatskin tumor, which, furthermore, 6 years later, underwent a pancreaticoduodenectomy for a metachronous carcinoma of the ampulla of Vater. The management and outcomes were discussed in the reported case, along with a literature review of the previously published patients. In conclusion, a metachronous periampullary carcinoma after resection of a Klatskin tumor should be distinguished from a loco-regional recurrent disease. While most of the patients with recurrences are suitable to only chemotherapy and/ or radiotherapy, a second curative-intent surgery (i.e., pancreaticoduodenectomy) is feasible in the largest part of the patients with a metachronous cancer, with good long-term outcomes.

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Key words: hilar cholangiocarcinoma; metachronous neoplasms, ampulla of Vater carcinoma; pancreaticoduodenectomy

Introduction

Hilar cholangiocarcinoma (Klatskin tumor) is a rare neoplasm, but the most frequently encountered type of cholangiocarcinoma (1,2). A Klatskin tumor is characterized by a slow growth rate and late metastasis, with a particular propensity for local invasion in major vascular structures of the hepatic pedicle and intrahepatic bile ducts; thus, only a palliative, non-surgical treatment is possible in most of the patients (3,4).

Although a Klatskin tumor has the worst prognosis of all cholangiocarcinomas (1,5), resection represents the single hope for a long-term survival in these patients (1,6). The median survival time in a patient diagnosed with a Klatskin tumor is less than 6 months without any kind of treatment (7), while for the patients with a curative-intent surgery the median survivals were reported between 19 months and 39 months (3,6).

A curative-intent surgery for Klatskin tumor implies bile duct resection, hepatectomy and loco-regional lymph nodes dissection (6,8). This aggressive surgical approach, that includes usually a major hepatectomy, was associated with significant morbidity and mortality rates (3), but with improved survivals (4,6).

Margins negative resection represents the most important determinant for both disease-free and overall survivals after surgery for Klatskin tumors (3,4,6).

Recurrence of the disease represents a common feature after curative-intent surgery for Klatskin tumors, and it was observed in 64% - 71% of the patients (3,4,8). Furthermore, the median disease-free survival time after curative-intent surgery for Klatskin tumor was reported between 14 months and 17 months (3,4,8).

A local-only recurrence after surgery for Klatskin tumors is uncommon, while most of the patients will develop distant metastases, with or without local disease (3,4,8). Recurrence of the disease after resection of Klatskin tumor allows only a non-surgical (i.e., chemotherapy and/ or radiotherapy), palliative treatment in the largest part of the patients (3,4,8).

Despite the poor prognosis of patients resected for Klatskin tumors, long-term survivors (i.e., ≥ 5 years) were previously reported (3,4,6,8). However, the development of a second bile duct cancer after resection of a Klatskin tumor is exceptional (9,10) and the management of these patients was poorly documented.

Hereby, it is presented the case of a patient who underwent a bile duct resection, along with left hemi-hepatectomy and loco-regional lymph nodes dissection, for a type IIIB Bismuth-Corlette Klatskin tumor, which, furthermore, 6 years later, underwent a pancreaticoduodenectomy for a metachronous carcinoma of the ampulla of Vater. The management and outcomes were discussed in the reported case, along with a literature review of the previously published patients.

Case report

A 32-year-old male, without any significant medical history, presented in an emergency setting, in another surgical unit, in

February 2005, for jaundice with cholangitis, and weight loss. The patient underwent a cholecystectomy with exploration of the common bile duct and a T-tube insertion for a presumed gallbladder lithiasis and secondary bile duct stenosis. Postoperatively, the jaundice aggravated and the patient was reassessed in another hospital gastroenterology unit. A magnetic resonance examination was performed showing a hilar stenosis with dilatation of the intrahepatic bile ducts, predominantly on the left side of the liver (Fig. 1, K). The patient was furthermore referred to our surgical unit. The serum biochemical laboratory profile showed the following abnormalities: cholestasis – total bilirubin = 13.8 mg/ dl (normal range, 0.1 – 1.0 mg/ dl), direct bilirubin = 8.5 mg/ dl (normal range, 0 – 0.4 mg/ dl), alkaline phosphatase = 1 137 U/ l (normal range, 50 – 110 U/ l); hepatic cytolysis – aspartate amino-transferase = 87 U/ l (normal range, < 45 U/ l); alanine amino-transferase = 109 U/ L (normal range, < 54 U/ l); increased leukocyte number (10 100/ microliter). The CA 19-9 serum level was within the normal limits.

In March 2005 the patient was submitted to surgery, and the diagnosis of a type IIIB Klatskin tumor was established, without loco-regional invasion or distant metastases. A common bile duct resection along with a left hemi-hepatectomy and loco-regional lymph nodes dissection was performed (Fig. 1, B). The biliary reconstruction was made with a single right bile duct inserted in a Roux en Y jejunal loop. The pathology report showed a 1 cm, nodular type, well-differentiated cholangiocarcinoma, T2, N0 (stage II according to the 7th edition of the TNM classification of the American Joint Committee on Cancer), without perineural invasion. The operative specimen was considered as margins negative resection.

The postoperative outcome was uneventful, and the patient was discharged on the postoperative day 11.

Adjuvant chemotherapy was performed (6 cycles, GEMOX scheme). The follow-up of the patient included clinical examination, bioumoral tests (including CA 19-9 serum level) and computed tomography examinations every 3 months during the first 2 years, and every 6 months in the remaining time to 5 years after surgery. No abnormalities were detected during the follow-up period.

In April 2011, the patient presented in an emergency setting, at our hospital gastroenterology unit, with nausea and vomiting. Bioumoral stands severe hypokalemia – K = 1.8 mEq/ l (normal range, 3.5 – 5.1 mEq/ l), mild renal dysfunction – serum urea level = 63 mg/ dl (normal range, < 45 mg/ dl), serum creatinine level = 1.2 mg/ dl (normal range, 0.6 – 1.1 mg/ dl). No other abnormalities were noted, including the CA 19-9 serum level. An abdominal computed tomography examination observed a tumor in the area of the ampulla of Vater, without any distant metastases (Fig. 1, C). Upper endoscopy highlights ulceration in the area of the ampulla of Vater. After a short preoperative rebalancing of the electrolytes, the patient was submitted to surgery.

Intraoperatively, the diagnosis of an ampulla of Vater tumor was confirmed, without local invasion or distant metastases, and a Whipple pancreaticoduodenectomy was

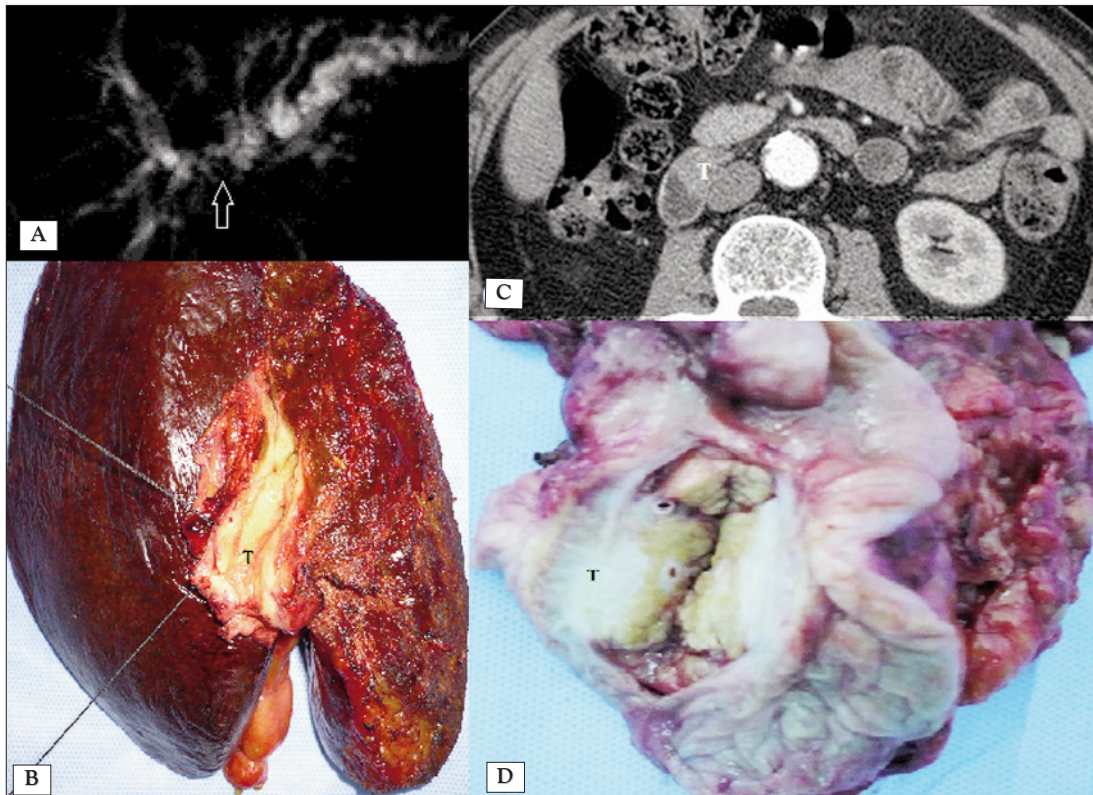


Figure 1. (A) Magnetic resonance imaging showing obstruction of the biliary carrefour due to a Klatskin tumor (white arrow), predominantly extending on the left side, with secondary bile duct dilatation; (B) Extrahepatic common bile duct resection with left hemi-hepatectomy for a type III Bismuth-Corlette Klatskin tumor (operative specimen; T – tumor); (C) Computed tomography imaging showing a tumor (T) in the area of the ampulla of Vater; (D) Pancreaticoduodenectomy for an ampulla of Vater carcinoma (operative specimen; T – tumor)

performed (Fig. 1, D). The reconstruction after resection preserved the previously cholangio-jejunal anastomosis, with the implantation of the distal pancreatic stump into the jejunum and a gastro-jejunal anastomosis. The pathology report showed a 3 cm, well-differentiated ampullary carcinoma, T3, N0 (stage IIa according to the 7th edition of the TNM classification of the American Joint Committee on Cancer). The operative specimen was considered as margins negative resection.

The postoperative outcome was uneventful, except for a grade B pancreatic fistula, and the patient was discharged on the postoperative day 18.

Adjuvant chemotherapy was performed (6 cycles, Gemcitabine). During the follow-up, at 1 year after surgery, the patient presented with minor cholestasis, without any clinical symptoms or signs. The magnetic resonance examination revealed dilatation of the intrahepatic bile ducts and a stenosis at the level of the cholangio-jejunal anastomosis. A percutaneous internalized biliary drainage was performed with an uneventful outcome (Fig. 2, A).

In December 2013 the patient presented with abdominal distension and the computed tomography examination revealed recurrence at the hepatic level and peritoneal car-

cinomatosis with ascites (Fig. 2, B and C). A tube for ascites drainage was percutaneously mounted, under ultrasound control. The performance status of the patient did not allow any chemotherapy and only a best supportive care was possible. The patient died in February 2014 with liver insufficiency, at almost 9 years after resection of the Klatskin tumor, and at almost 3 years after resection for ampullary carcinoma.

Discussion

Surgical approach for the extrahepatic biliary cancers is tailored to tumor number, location and extent (1,8,10). A curative-intent surgery for a Klatskin tumor implies a liver resection while pancreaticoduodenectomy represents the single hope for cure in periampullary carcinomas (8). For Klatskin tumors, the extent of liver resection is mainly guided by the Bismuth-Corlette classification (6).

The resection rate is about 67% for bile duct cancers and 91.2% for the ampulla of Vater carcinoma (11). Furthermore, the prognosis of patients resected for Klatskin tumors is different compared with the ampullary carcinomas: 5-years survival rates 26% vs. 56% (11).



Figure 2. (A) Percutaneous internalized biliary drainage for a cholangio-jejunal anastomosis stenosis (cholangiographic aspects; the white arrow marks the cholangio-jejunal anastomosis); Computed tomography imaging aspects showing (B) recurrence of the disease (R) in the liver and (C) ascites secondary to peritoneal carcinomatosis

Few studies have previously documented the presence of synchronous or metachronous extrahepatic bile duct cancers (9,10,12-19). The reported cases included mostly synchronous bile duct and gallbladder cancers, with or without associated pancreaticobiliary maljunction (12-14,17,20). Several studies have reported an incidence of synchronous extrahepatic bile duct cancers of 1.5% - 9% (13,14,16,17). In a large recent series of patients resected for biliary tract cancer at a single surgical center in Nagoya, only 0.7% presented synchronous bile duct cancers (8). It appears that multicentric bile duct cancers have distinct clinical and pathological features: are more likely to have a papillary pattern, presents in earlier stages and negative lymph nodes are more frequently encountered (16). Furthermore, a multicentric bile duct cancer does not preclude a curative-intents surgery, and the long-term outcome is not different compared to a single bile duct cancer (17).

At the end of 2014, only 31 patients with metachronous cancer of the bile duct were reported in the literature (9,10,15). The largest part of these patients has had a gallbladder or a middle/ distal bile duct cancer as the first site of the tumor and the interval between the resection of the first tumor and resection of the metachronous tumor varied between 3 months

and 13 years (9,10,15). The incidence of metachronous extrahepatic bile duct cancers is reported to be around 1% - 2.4% (9,16).

Up to now, only 10 patients resected for a Klatskin tumor who furthermore developed a metachronous bile duct or ampulla of Vater cancer were previously reported (9,10,21,22), as shown in Table 1. Interestingly, there is only one reported patient resected for a type IIIa Klatskin tumor who developed 2 years later a metachronous ampulla of Vater carcinoma that was treated with a pancreaticoduodenectomy; the patient survived 3 years after the resection of the first cancer (9). Pancreaticoduodenectomies have been previously demonstrated to be safe and effective for metachronous periampullary malignancies, albeit in a very limited number of patients (9,10,23).

A metachronous bile duct cancer should be clearly distinguished from a loco-regional recurrent disease (10) because the treatment approach and prognosis might be different. Recurrences after resection for extrahepatic bile duct cancers are widely considered to have a poor prognosis because a second curative-intent surgery is not possible for the largest part of these patients (8,24). In Nagoya experience, only 10%

Table 1. Data from the literature of patients resected for a Klatskin tumor; with metachronous biliary tract malignancies

Author, year	Age (years)/ Gender	Site of 1 st cancer	Surgical approach	Pathology	Site of 2 nd cancer	Surgical approach	Pathology	Interval between the tumors	Status ^a
Todoroki, 1993(21)	67/ F	HC type IIIb	EBHDR + LH	NA	IHC	RAS	NA	13y	Alive at 16y5mo, DF
Yoon, 2005(22)	29/ F	HC type IIIb	EBHDR + RH	NA	DCBD	SBDR	NA	2y4mo	Alive at 3y1mo, DF
Kwon, 2014(10)	70/ F	HC type I	EBHDR	T1N0, R0	DCBD	PD	T3N0, R0	1y2mo	Alive at 7y2mo, DF
Kim, 2014	45/ M	HC type IIIa	EBHDR + RH	T2N0, R0	DCBD	PD	T3N1, R0	1y	DOD at 3y8mo
Kim, 2014(9)	63/ F	HC type IIIb	EBHDR + LH	T1N0, R0	DCBD	PD	T1N0, R0	2y2mo	Alive at 5y4mo, DF
Kim, 2014(9)	55/ M	HC type II	EBHDR + LR	T2N0, R0	DCBD	PD	T3N1, R0	1y9mo	DOD at 2y6mo
Kim, 2014(9)	67/ F	HC type IIIa	EBHDR + RH	T2N0, R1	AC	PD	T1N0, R0	2y1mo	DOD at 3y3mo
Kim, 2014(9)	63/ M	HC type IIIa	EBHDR + RH	T1N0, R0	DCBD	PD	T1N0, R0	3mo	Alive at 1y4mo, DF
Kim, 2014(9)	53/ M	HC type I	EBHDR	T1N0, R0	DCBD	PD	T1N0, R0	2y7mo	Alive at 3y7mo, DF
Kim, 2014(9)	65/ M	HC type I	EBHDR	T2N0, R0	DCBD	PD	T3N1, R0	3y	DOD at 4y6mo
Present case	32/ M	HC type IIIb	EBHDR + LH	T2N0, R0	AC	PD	T3N0, R0	6y1mo	DOD at 8y11mo

^atime from the resection of the first cancer; HC – hilar cholangiocarcinoma; IHC – intrahepatic cholangiocarcinoma; DCBD – distal common bile duct; AC – ampulla of Vater carcinoma; EBHDR – extrahepatic bile duct resection; LH – left hemi-hepatectomy; RH – right hemi-hepatectomy; RAS – right anterior sectionectomy; LR – liver resection not specified; SBDR – segmental bile duct resection; PD – pancreaticoduodenectomy; DF – disease-free; DOD – died of disease; NA – not available

of the patients who developed recurrences after resection for biliary tract cancer were suitable for a second surgical resection; the long-term survival of these patients was significantly better compared to the outcome of the patients with unresectable recurrences (8). Conversely, in most of the reported patients with metachronous bile duct cancer a second curative-intent surgery was possible with good long-term outcomes (9,10,15). Nevertheless, different pathogenic pathways were suggested for the two clinical entities: intraluminal tumor implantation for metachronous cancer and residual cancer cells at the surgical margins for local recurrences (9).

Finally, Kwon and co-workers have proposed a classification of the metachronous bile duct cancers according to the site of de novo neoplasm (10). However, the clinical usefulness of this classification remains to be demonstrated by future studies.

Conclusions

A metachronous perihilar carcinoma after resection of a hilar cholangiocarcinoma represents an exceptional pathology that should be distinguished from a loco-regional recurrent disease. While most of the patients with recurrences are suitable to only chemotherapy and/ or radiotherapy, a second curative-intent surgery (i.e., pancreaticoduodenectomy) is feasible in the largest part of the patients with a metachronous cancer, with good long-term outcomes.

Funding

None.

Conflicts of interest

None declared

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