

Main bile duct carcinoma management

Our experience on 38 cases.



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BACKGROUND: *Cholangiocarcinoma (CC) is rare malignant tumors arising from cells of the biliary tract. It presents some difficulties to diagnose, and is associated with a high mortality. Traditionally extrahepatic CC is divided into klatskin tumors, intermediate tract and distal or iuxtapapillar tumors according to its location within the biliary tree. CT, RM, PET may provide useful diagnostic information in those patients. Surgical resection is the only chance for cure, with results depending on selected patients and careful surgical technique. Liver transplantation could offer long-term survival in selected patients when combined with chemotherapy. Chemotherapy, radiation therapy, and external drainage remain as the only treatment for inoperable patients.*

MATERIAL AND METHODS: *The authors report their experience since 1997 inherent to 38 cases of extrahepatic CC, 21 of which were treated by surgery: their outcome has been evaluated.*

RESULTS: *Surprisingly four of them (2 with intermediate tract tumor and 2 with distal tract tumors) are still alive and apparently disease-free after 5 years since surgery. Moreover another one patient with papillar tumor has reached 5 years survival despite has undergone surgery two times.*

CONCLUSION: *Surgery remains the best chance for long-term survival, and lymph node status is the most important prognostic factor following R0 resection*

KEY WORDS: CBD carcinoma, Cholangiocarcinoma, Main bile duct cancer.

Introduction

EPIDEMIOLOGY

In Western Europe, cholangiocarcinoma (CC) is a rare tumor whose incidence is valued in approximately 2 - 4 new cases for 100,000 inhabitants a year.

Those malignancies represent approximately 2% of all the malignant tumors in autoptic findings.

Adenomas, recidivant cholangitis, malformations of CBD, ulcero-hemorrhagic colitis, and sclerosant cholangitis have been assumed as predisposing conditions.¹

In such eveniences, the risk of neoplastic degeneration increases from 1% of infancy to 14% of the adult age. In Far East a not negligible role is played from clonorchis sinensis and opistorchis viverini's infections.²

Cholangiocarcinomas represent an heterogenous group of malignancies that includes the intraepatic colangio-carcinoma (or peripheral carcinoma), colangiocarcinoma of the gallbladder (or carcinomas of accessory biliary tract), iuxta-ilars tumors (Klatskin's tumors), tumors of the epatocholedocus (intermediate biliary tract), distal tumors and tumors located on Vater's papilla.

The last ones are reunited above all because of their common surgical destiny: the necessity of duodenocefalopancreasectomy. Although, in selected cases with small papillary tumors, an endoscopic resections could be performed.³

We are excluding from this review the hepatic and gallbladder tumors.

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LOCATION

Hilar cholangiocarcinoma involves the system of the hilar plate, constituted from hilum plate, cystic plate and umbilical plate, fused together with epatoduodenal ligament.

According to Bismuth anatomopathological classification we can distinguish:

- **type I tumors:** the neoplasia is located at least 1 cm under the confluence.
- **type II tumors:** or true confluence tumors which interrupt left and right bile duct confluence.
- **type III tumors:** which widely extends from the convergence to only one of the two hepatic emisystems.
- **type IV tumors:** wich start from the convergence and widely spread towards both emisystems

An additional problem other than ductal extension is the involvement of the vascular structures of the hilum.

The tumors of intermediate tract are localized between 1-2 cm under the convergence and superior border of retroduodenal portion; generally cystic duct enter in the middle of this tract.

Ampullary tumors: while distal tumors of the CBD have a similar clinical behaviour to the previous ones, ampullary tumors introduce some peculiarities. Their diagnosis is often relatively early and easy: it could be done endoscopically, and sometimes in "N0" selected cases may be possible trying a local removal.

We must underline that some ampullary tumors may arise from the inner portions of the ampoule covered from biliopancreatic mucosa or from the external portions, covered of duodenal mucosa: the pattern of expressed markers as the immunohistochemical profile changes: we will find CA19-9 marker, keratina 7+, keratina 20-, MUC2- on tumors biliary mucosa related and CEA, keratina 7- keratina 20+, MUC2+ on tumors duodenal mucosa related.

Material and methods.

We will examine cases of carcinoma treated that occurred mainly in the hilar area, common bile duct, and tumors interesting papillary area.

Since 1997 we have experienced 38 cases of colangiocarcinomas of the VBP.

Sixteen (16/38) were localized in the hilum, eleven (11/38) in the intermediate biliary tract and eleven (11/38) in the distal cholodocus or in the papilla. They have been studied with ECO, TC and CholangioRM and twentyone, judged operable, underwent surgery. Seventeen patients, who weren't surgically treated, were treated with percutaneous stent and/or chemotherapy. They all died within two years since diagnosis.

HILAR TUMORS

Eight (8/16) patients with Klatskin tumors underwent surgery.

We performed a resection of biliary confluence with partial ablation of the V, IV and I segments of the liver, linphoadenectomy and biduct to jejunum anastomosis on a defunctionalized bowel tract in five cases (type II Bismuth).

Two patients (type IIIb Bismuth) underwent to left hepatectomy and left hepatic duct to jejunum anastomosis. One patient (IIIa Bismuth) has not been judged "radically treated" because of local extension and vascular involvement so the percutaneous stent, previously placed, has not been removed.

INTERMEDIATE TRACT TUMORS

Six (6/11) patients with tumors localized in the cholodocus have been preoperatively judged operable.

All patients underwent to CBD, gallbladder and cystic duct resections hepatic peduncle linfoadenectomy , and hepatic duct to jejunum anastomosis.

DISTAL TRACT TUMORS OR AMPULLARY TUMORS

Seven cases (7/11) with tumors localized in the distal CBD tract or interesting ampulla area underwent surgery: 4 underwent to cefaloduodenopancreasectomy (2 Whipple and 2 Traverso-Longmire), 3 were treated by hepatic-jejunum anastomosis.

Results

Morbidity and survival have been evaluated.

All the tumors of klatskin are passed away within two years of follow up.

Three of six patients who underwent surgery with radical attempt have manifested a recidiva after 7-15 months, while one of patients who underwent hepatectomy died after eight months for metabolic unbalances. Two patients who underwent resection with tumors arising in the middle tract of CBD are alive to 6 and 5 years since surgery. The patient who underwent to kehr placement died 7 months after surgery.

The patients with tumors on the distal tract of CBD or

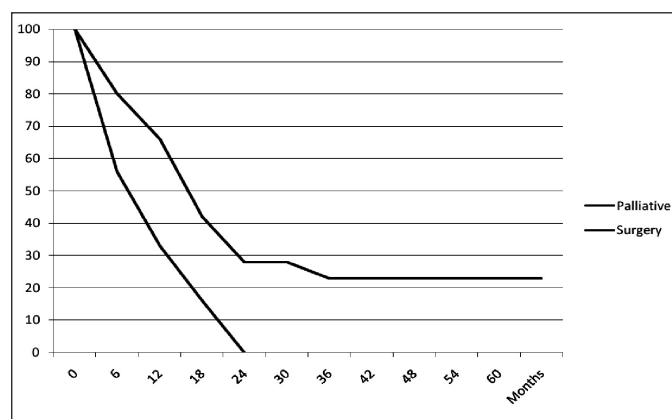
TABLE 1

Cholangiocarcinomas	Hilum	Intermediate	Distal or papilla	Total
Surgery	8	6	7	21
Palliative	9	4	4	17
Total	17	10	11	38

TABLE II

Overall survival	12 months	24 months	36 months	5 years
Hilar	6/8	1/8	0/8	0/8 (0%)
Intermediate	3/6	2/6	2/6	2/6 (33%)
Distal / papilla	5/7	3/7	3/7	3/7 (42%)
Total	66% (14/21)	28.5% (6/21)	23% (5/21)	23% (5/21)

Overall survival:



iuxta-papillar who underwent derivative surgery are deceased, except the last one, who underwent surgery only 13 months ago.

In the group of patients treated by cefaloduodenopancreasectomy one died for repeated post-operative hemorrhages from acquired coagulation deficit.

One patient with a 6 mm tumor of the papilla (in this case we have evaluated the opportunity of endoscopic resection) underwent surgery. After cefaloduodenopancreasectomy were not found linfonodal metastases; 34 months later he developed hepatic, lomboaortic and cutaneous metastases. He underwent surgery again and we performed left hepatectomy, lomboaortic linfoadenectomy and cutaneous metastasectomy. Other two patients (N0) who underwent to cefaloduodenopancreasectomy, have demonstrated no lymphnodes involvement and are alive respectively 5 and 6 years later.

Discussion

DIAGNOSTIC PROBLEMS

These malignancies of our experience became clinically evident by the growing jaundice with ematochemical signs of cholestasis.

Clinical diagnosis is entrusted by echography, TC and RM with the purpose of discovering tumor localization along the biliary tract, disease's spread and its relationships to the hilum elements.

Diagnosis of small lesions especially those arising in intermediate CBD tract of the VBP may be difficult because of unstable icterus.

Lesions arising in the papilla may be discovered by endoscopic findings while ERCP is useful in diagnosis of distal lesions.

We have to underline the role of cytology with thin aspiration needle: according to Dewitt (2006)

it can represent a sensitive method for the diagnosis of hilar lesions, even if the low prediction value does not concur to exclude the malignant nature in case of negative finding.⁴

Another diagnostic method is the ERCP brushing, not only for the traditional cytology but also for the study of the genetic alterations found on the esfoliated cellular material like the presence of K-ras and the mutations of the gene 17P53 gene implied in suppressing cellular proliferation, DNA correction systems recruitment and apoptosis.

THERAPEUTIC PROBLEMS

Resectability

Surgical treatment offers nowadays a real opportunity of treatment with radical attempt, but at the moment of the diagnosis only 20 - 25% of the patients can be surgically treated.

According to Blom (2001) and according to Valceanu (2003) only one 1/3-1/4 of patients are susceptible of resection and in only on these we are able to modify the prognosis.

Some specialized centers (Launois, 1999) extend surgical treatment over 50 % of patients however with an increase of mortality of 12.5%.⁷

Some Japanese authors (Hasegawa, 2007) produce better results in perioperative mortality (2%) and morbidity; however they report an high percentage of recidives (39.4%).⁸

According to Wang (1997) resectability in the three areas (high, medium and low parts of the VBP) demonstrate promising percentages (respectively of 50%, 50% and 71.4%), while the diagnostic reliability of sonography and TAC diagnoses are up to 95%: although high are in his experience percentages of recidiva (73.9% to a year and 100% to 3 years).⁹

Techniques

There are some difficulties inherent therapeutic guidelines of hilar tumors especially when related to the 4

types in Bismuth and Corlette's classifications (I, II, IIIa, IIIb, IV).

Surgical options, according to Seyama Y, Makuuchi M, vary from resection of CBD, confluence resection, a more or less extended IV, V or I segmentectomy, linfoadenectomy and reconstruction by biduttoepaticodigiunostomy, to confluence resection and left or right hepatectomy, linfoadenectomy and hepatic duct to jejunum anastomosis up to orthotopic liver transplant (OLT) especially for intrathepatic widespread lesions.^{10,11,12}

Outcome

DeOliveira ML et al (2007) evaluated long term survival and prognostic factors on 564 patients:

the median survivals for R0-resected intrahepatic, perihilar, and distal tumors were 80, 30, and 25 months, respectively, and the 5-year survivals were 63%, 30%, and 27%, respectively.

They concluded that R0 resection remains the best chance for long-term survival, and lymph node status is the most important prognostic factor following R0 resection.¹³

Miyazaki M, Kato A (2007) evaluated how combined vascular resection in operative resection for hilar cholangiocarcinoma affects the outcome of patients: their multivariate analysis on 161 cases suggested portal vein and hepatic artery involvement as poor and independent prognostic factors. They concluded that portal vein resection is an acceptable opportunity despite the increasing operative risk but combined portal vein and hepatic artery resection cannot be justified.¹⁴

According Lindell (the 2000), survival in these patients, despite the progress in the treatment, has not improved during the last few years.¹⁵

We think that, even if the treatment of the tumors of klatskin can give satisfactory results, better results can be obtained in CBD small lesion treatment. The lesions of the papilla, generally, but not always as demonstrates our experience, prelude to better prognosis, and should be treated by DCP even if, in selected cases and with a consent truly informed, endoscopic papillectomy may find an indication.¹⁶

Complementary and palliative therapy

Patients with unresectable malignancies have the worst prognosis with a mean survival time of less than a year: the aim is palliative treatment of jaundice through stents percutaneously or endoscopically placed. Otherwise bilio-digestive anastomosis is another chance.

Complementary treatments, with chemio (5-FU, gemcitabina) and radiotherapy (internal and external) can obtain only modest results: Hughes et al studied the effects of adjuvant chemoradiation on a group of 32 patients affected by distal bile duct carcinomas: patients who underwent surgery and adjuvant chemoradiation

had significantly longer survival (36.9 months vs. 22 months; $p < 0.05$). Overall survival was significantly longer for both lymph node negative and lymph node positive patients.^{17,18} There are only few reported cases of biliary tract carcinoma in elderly patients in whom gemcitabine chemotherapy induced complete remission.¹⁹

Conclusions

Despite the progresses reached in diagnostic field and surgical techniques, the tumors of the VBP maintain their malignant behavior, because of their silent clinical evolution that became evident only for the icterus, and because of the importance of the structures often involved. Only identification of the risk factors could lead to extend procedures of endoscopic screening with the purpose of reveal cytological alterations in biliary citologic findings of morphologic type or genetic type that are the only early spies of malignancies.

Riassunto

Il colangiocarcinoma (CC) è un raro tumore maligno che trae origine dalle cellule del tratto biliare. Presenta alcune difficoltà diagnostiche e si associa ad una elevata mortalità.

Classicamente i CC extraepatici si suddividono in tumori di klatskin, del tratto biliare intermedio e distale o iuxtapapillari secondo la relativa localizzazione nell'ambito dell'albero biliare.

CT, RM, PET possono offrire utili informazioni diagnostiche in questi pazienti. La resezione chirurgica è l'unica possibilità di cura, con risultati che dipendono dalla selezione dei pazienti e dalla accuratezza della tecnica chirurgica. Il trapianto epatico potrebbe offrire una sopravvivenza di lungo periodo in pazienti selezionati se combinato con chemioterapia. Chemioterapia, terapia radiante ed il drenaggio biliare esterno rappresentano gli unici trattamenti per i pazienti non operabili.

Gli Autori riferiscono la loro esperienza a partire dal 1997 che riguarda 38 casi di CC extraepatico, 21 dei quali vennero trattati chirurgicamente, e valutano i risultati.

Sorprendentemente quattro di essi (2 con CC del tratto intermedio e 2 con tumore del tratto distale) sono attualmente vivi ed apparentemente liberi da malattia dopo 5 anni dal trattamento chirurgico. Inoltre un altro paziente con tumore della papilla di Vater ha raggiunto una sopravvivenza di 5 anni nonostante sia stato sottoposto a trattamento chirurgico due volte.

Conclusioni: la chirurgia rimane la migliore possibilità per raggiungere una sopravvivenza a lungo termine, e lo stato linfonodale rappresenta il più importante fattore prognostico dopo una resezione R0.

References

- 1) Cavallaro V, Mirone I, Lizzio A, Cavallaro A, Pennisi S, Cammisuli F: *Biliary tract carcinoma. Case report.* Minerva Chir, 2002; 57(2):197-202.
- 2) Lim MK, Ju YH, Franceschi S, Oh JK, Kong HJ, Hwang SS, Park SK, Cho SI, Sohn WM, Kim DI, Yoo KY, Hong ST, Shin HR: *Clonorchis sinensis infection and increasing risk of cholangiocarcinoma in the Republic of Korea.* Am J Trop Med Hyg, 2006; 75(1):93-96.
- 3) Alberts SR, Gores GJ, Kim GP, Roberts LR, Kendrick ML, Rosen CB, Chari ST, Martenson JA: *Treatment options for hepatobiliary and pancreatic cancer.* Mayo Clin Proc; 2007; 82(5):628-37.
- 4) DeWitt J, Misra VL, Leblanc JK, McHenry L, Sherman S: *EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results.* Gastrointest Endosc, 2006; 64(3):325-33.
- 5) Blom D, Schwartz SI: *Surgical treatment and outcomes in carcinoma of the extrahepatic bile ducts: the University of Rochester experience.* Arch Surg, 2001; 136(2):209-15.
- 6) Vâlceanu D, Nica C, Olariu S, Blaj S. Chirurgia (Bucur): *Our experience regarding neoplasms of the extrahepatic bile ducts.* 2003; 98(3):237-41.
- 7) Launois B, Terblanche J, Lakehal M, Catheline JM, Bardaxoglou E, Landen S, Campion JP, Sutherland F, Meunier B: *Proximal bile duct cancer: high resectability rate and 5-year survival.* Ann Surg, 1999; 230(2):266-75.
- 8) Hasegawa S, Ikai I, Fujii H, Hatano E, Shimahara Y. *Surgical resection of hilar cholangiocarcinoma: analysis of survival and postoperative complications.* World J Surg, 2007; 31(6):1258-265.
- 9) Wang S, Han B, Cai J: *Surgical treatment of extrahepatic bile duct carcinoma.* Zhonghua Yi Xue Za Zhi. 1997; 77(12):944-47 Chinese. PMID: 9772582:
- 10) Seyama Y, Makuuchi M: *Current surgical treatment for bile duct cancer.* World J Gastroenterol, 2007; 13(10):1505-515.
- 11) Ishihara S, Miyakawa S, Takada T, Takasaki K, Nimura Y, Tanaka M, Miyazaki M, Nagakawa T, Kayahara M, Horiguchi A: *Status of surgical treatment of biliary tract cancer.* Dig Surg, 2007; 24(2): 131-36.
- 12) He XS, Zhang S, Zhu XF, Wang DP, Ma Y, Wang GD, Ju WQ, Wu LW, Huang JF: *Orthotopic liver transplantation with hepatopancreatoduodenectomy for hilar cholangiocarcinoma.* Chin Med J (Engl), 2007; 120(3):251-53.
- 13) DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, Choti MA, Yeo CJ, Schulick RD: *Cholangiocarcinoma: Thirty-one-year experience with 564 patients at a single institution.* Ann Surg, 2007; 245(5):755-62.
- 14) Miyazaki M, Kato A, Ito H, Kimura F, Shimizu H, Ohtsuka M, Yoshidome H, Yoshitomi H, Furukawa K, Nozawa S: *Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not?* Surgery, 2007; 141(5):581-88.
- 15) Lindell G, Hansson L, Dawiskiba S, Andersson R, Axelson J, Ihse I: *Operations for extrahepatic bile duct cancers: Are the results really improving?* Eur J Surg, 2000; 166(7):535-39.
- 16) Yamada S, Fujii T, Sugimoto H, Takeda S, Inoue S, Nomoto S, Kanazumi N, Nakao A: *A proposal of an appropriate surgical approach for cancer of the ampulla of Vater: retrospective analysis of 73 resected cases.* Hepatogastroenterology, 2007; 54(73):10-14.
- 17) Shimoda M, Kubota K: *Multi-disciplinary treatment for cholangiocellular carcinoma.* World J Gastroenterol, 2007; 13(10):1500-504.
- 18) Hughes MA, Frassica DA, Yeo CJ, Riall TS, Lillemoe KD, Cameron JL, Donehower RC, Laheru DA, Hruban RH, Abrams RA: *Adjuvant concurrent chemoradiation for adenocarcinoma of the distal common bile duct.* Int J Radiat Oncol Biol Phys, 2007; 68(1):178-82.
- 19) Nitta S, Nagayama K, Sakai Y, Kusano F, Tazawa J: *Biliary tract carcinoma in elderly patients in whom gemcitabine chemotherapy induced complete remission. A report of two cases.* Gan To Kagaku Ryoho, 2007; 34(6):941-43.

