

## MALIGNANT TUMORS OF THE EXTRAHEPATIC BILE DUCTS – DO THEY REMAIN A CHALLENGE?

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Reviewed by: Assoc. Prof. R. Madjov, MD, PhD

### ABSTRACT

**Background/ Aim:** Though there is an improvement in the diagnostics and treatment of extrahepatic bile duct carcinoma (EHBDC) the postoperative results are still unsatisfactory. The aim of the study was to analyse the experience of the authors' institution in the treatment of EHBDC and to compare the results according to the tumor's location and stage and the surgical procedure performed. **Material and methods:** From Jan.,1989 to Jan.,2005, 1024 patients with EHBDC (incl. periampullar ones) received surgical treatment. The study was retrospective based on clinical, laboratory, instrumental, intraoperative and pathological data. **Results:** The male/female ratio was 3/2 and 44.53% of all patients were above 60 years of age. Most of the EHBDC's were located in the distal part – 680 cases (66.41%). Klatskin tumors ranked second – 144 cases (14.06%). Radical, palliative and explorative procedures were performed in 28.42%, 66.11% and 5.47% respectively. Radical resectability showed dependence on the tumor's location and stage. The early morbidity and mortality rates were 31.84% and 14.16% respectively. The median long-term survival (in months) after radical procedures was 24 for Klatskin tumors, 17 for carcinoma of the middle EHBDC and 40 for periampullary tumors and these figures were significantly worse after palliations. **Conclusions:** 1. EHBDC is observed more often in patients above 60 years of age, it has aggressive biology and poor prognosis; 2. Reliability of US, ERCP, CT-scan and MRI in cases of EHBDC exceeds 95%; 3. More than 70% of the patients with EHBDC are diagnosed in stage III and IV limiting radical resectability; 4. EHBDC's of the middle and distal parts are more often suitable for radical resections than proximal tumors.

**Keywords:** carcinoma, extrahepatic bile ducts, obstructive jaundice, surgical treatment

### INTRODUCTION

The first definition of bile duct cancer is credited to Fardal (1840). (1) But more than a century after that G. Klatskin (1963, New Haven, Connecticut) published the first profound and detailed study on 13 cases of malignant tumors of the proximal part of the extrahepatic biliary tree. (2) The author described this type of cancer as small, localized and strictly confined to the common hepatic duct, rarely metastasizing, and in some cases leading to purulent cholangitis and/or acute hepatocellular failure. (2) Nowadays tumors of the extrahepatic bile ducts (EHBDC) are classified according to their location after W.P.Y. Longmire (Fig.1). (3) The classification of Bismuth and Corlette is particularly used for carcinomas of the proximal part of the EHBDC – the so called "Klatskin" tumors (Fig.2). (4) The incidence rate of extrahepatic bile duct cancer (EHBDC) increases permanently during the last three de-

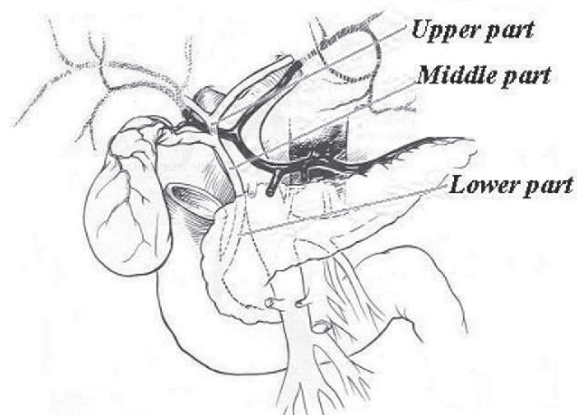


Fig. 1. The classification of the main parts of the extrahepatic bile ducts after W.P.Y. Longmire (1973)

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ades but this might be a result of improved diagnostics. (1,5,6,11) Treatment of EHBDC has also marked a progress due to advanced surgical techniques, endoscopic biliary stenting, interventional radiology and chemo- and

radiation therapy.(1,7-17) However despite these achievements EHBDC remains a challenge to all the specialist from the multidisciplinary team dealing with this problem.

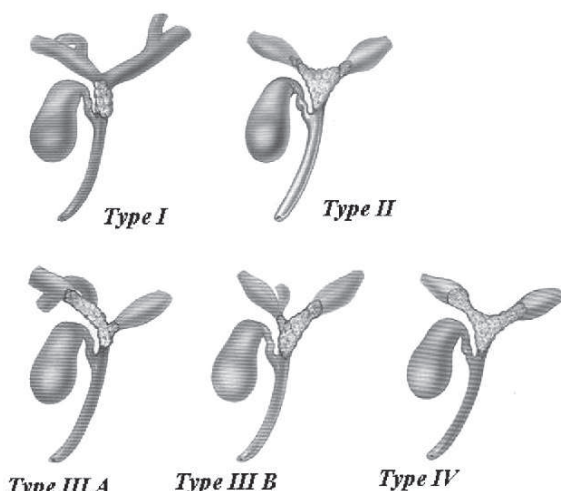


Fig. 2. The classification of Klatskin tumors after Bismuth and Corlette (1975). Type I - common hepatic duct; Type II - common hepatic duct + bifurcation; Type III A - bifurcation + right hepatic duct; Type III B - bifurcation + left hepatic duct; Type IV - total

### AIM

To study the experience of the authors' institution in the diagnostics and treatment of patients with EHBDC and to analyse the early and late postoperative results and their dependence on the location of the tumor, its stage and the surgical procedure performed.

Table 1. Relative frequency of the location of EHBDC in our material

Location of the primary tumor	No of cases	%
Upper part of the EHBD (Klatskin tumors)	144	14,06
Middle part of the EHBD	53	5,18
Periampullary tumors:	680	66,41
1. Distal common bile duct	35	3,42
2. Ampullary and papillary tumors	53	5,18
3. Head of the pancreas	585	57,13
4. Duodenum	7	0,68
Total involvement of the EHBD	37	3,61
Gall bladder cancer infiltrating the hepato-duodenal ligament	110	10,74
Total	1024	100,00

### MATERIAL AND METHODS

From 01/01/1989 to 01/01/2005, 1024 consecutive patients with EHBDC including also periampullary tumors were diagnosed and treated at the Clinic of General, Liver and Pancreatic Surgery, University Hospital "Alexandrovska", Sofia. The distribution of cases according to the location of the primary tumor is demonstrated on Table 1.

The study was retrospective based on diagnostic and surgical methods and outpatient follow-up (once per three months during the first year and twice a year after that). Differences concerning morbidity and mortality rates and long-term survival were compared using the chi-square test and Fisher's exact test. A "p"-value less than 0.05 was considered significant.

### RESULTS

Among all the patients 619 (60.45%) were male and 405 (39.55%) female. The male/female ratio was approximately 3/2 ( $p < 0.001$ ). The mean age of the whole group was 60.7 +/- 18.3 years, 61.9 and 58.7 for men and women respectively ( $p > 0.05$ ). The age above 60 years was the most often seen (44.53%) while only 23.73% of the patients were under 50 ( $p < 0.01$ ).

The analysis of data concerning the frequency of different locations showed the prevalence of periampullary tumors - 680 cases (66.41%). Klatskin tumors ranked second with a number of 144 cases (14.06%). Carcinoma of the middle part of the EHBD was observed in 53 patients (5.18%) and total involvement of the EHBD in only 37 patients (3.61%) ( $p < 0.001$ ).

Table 2. Clinical presentation of EHBDC

Clinical symptoms and syndromes	No of patients	%
Obstructive jaundice	981	95,80
Pain and discomfort in the right hypochondrium	868	84,76
Epigastric pain, nausea, vomiting	496	48,43
Weakness, loss of appetite and body weight	192	18,75
↑T°	171	16,70
Other nonspecific symptoms	98	9,57

The leading clinical symptoms and syndromes (Table 2) and the laboratory data (Table 3) were the typical ones for malignant biliary obstruction.

We used routinely ultrasound (US), ERCP, computed tomography (CT)-scan, magnetic resonance (MR)-cholangio-pancreatography and intraoperative

cholangiography for establishing the final diagnosis with a high rate of reliability, exceeding 95% (Table 4).

Radical surgical procedures were received by 291 patients (28,42%), palliative – by 677 patients (66,11%) and we performed only explorative laparotomies in 56 cases (5,47%) (Table 5). The type of the surgical operation corresponded to the stage of the EHBDC. The instrumental and intraoperative data as well as the pathological study showed that 792 tumors (77,34%) were in stage III and IV.

Table 3. Laboratory data in patients with EHBDC

Laboratory sign	No of patients	%
↑ serum bilirubin	994	97,07
↑ alkaline phosphatase	962	93,94
↑ GGT	853	83,30%
↑ ASAT; ↑ ALAT	496	48,93
Secondary anaemia	704	68,75
Hypoalbuminemia	518	50,59
Disturbed coagulation	498	48,63

Method	Total No of investigations/ No of confirmed diagnosis	Reliability (%)
US	1023/977	95,50
ERCP	467/463	99,14

Resectability depended also to the location of the carcinoma. Tumors of the middle part of the EHBDC were radically removed in 69.81% (37 from all the 53 cases) and tumors of the distal common bile duct, the ampulla and the papilla of Vater (i.e. periampullary tumors excluding pancreatic and duodenal cancer) – in 67.04% (59 from all the 88 cases).

There were 41 radical resections (22,05%) for Klatskin tumors and 24 of them (16,66%) included liver and/or vascular resections.

The total number of duodeno-pancreatectomies in cases of periampullary tumors was 193 (184 Whipple resections and 9 pylorus preserving Traverso-Longmire procedures).

The early postoperative mortality rate was 14.16% (145 cases) in the whole group. It was higher in explorative laparotomies – 28.57% (p<0,05). The main cause for fatal outcome was progression of the hepatic dysfunction leading to hepatic failure.

The morbidity rate was 31.84% (326 cases). The most common specific complications were persistent cholangitis, biliary leakage and acute upper gastrointestinal tract bleeding, necessitating re-operation in 23 cases (2.25%).

Table 5. Types of the surgical procedures according to the location of EHBDC

Type of the procedure/ Location of the tumor	Radical No (%)	Palliative No (%)	Explorations No (%)	Total
1. Klatskin tumors	41 (28,47%)	100 (69,44%)	3 (2,09%)	144
2. Middle part BDC	37 (69,81%)	16 (30,19%)	0	53
3. Periampullary tumors				
- ampulla, papilla, distal CBD*	58 (65,91%)	30 (34,09%)	-	88
- head of the pancreas	129 (22,05%)	432 (73,85%)	24 (4,10%)	587
- duodenum	6 (85,71%)	1 (14,29%)		7
4. Totally involved EHBDC	0	31 (83,78%)	6 (16,22%)	37

Table 6. Median survival according to the location of the tumor and the type of the surgical procedure

Location of the tumor	Radical procedure (survival in months)	Palliative procedure (survival in months)
Klatskin tumors	24	4,9
Middle part	17	11,5
Periampullary tumors incl. the distal CBD	40	10

\*CBD -common bile duct

The median survival rates according to the tumor's location and the type of the surgical procedure are demonstrated on Table 6. The differences between these data after radical and palliative operations proved to be statistically significant (p<0.01).

## DISCUSSION

The main characteristic features of EHBDC are those described by Klatskin. The tumor aggressiveness is due to the trend to vascular invasion and neural infiltration but the tendency to metastasise is little and sometimes even palliations may offer a satisfactory long-term survival. (1,7,8,10,11,19)

The right approach to these cases and the way of obtaining maximum benefit and good quality of life are still controversial. Now we shall focus on some current debatable problems concerning EHBDC.

Is it possible to establish the diagnosis "EHBDC" early?

The clinical signs of EHBDC are more or less specific but they are late. Tumor markers (CA 19-9 and CEA) are often normal (5,6). The diagnostics have been significantly improved due to the new methods routinely used in practice during the last 25-30 years - US, ERCP, CT and MR-cholangiopancreatography. (6,8,11) *However even nowadays about 70-75% of all cases are found in stage III and IV which determines the low rate of radical resectability and poor prognosis.* (7,11,14,18-20)

A possibility for early detection of EHBDC exists in the active outpatient follow-up of cases with a pre-cancer condition such as cystic dilation of the bile ducts, clonorchiasis, hepatolithiasis, sclerosing cholangitis, varieties of the hepatic artery and its main branches causing compression on the EHBD. (6)

Radical or palliative procedure should be preferred in EHBDC?

According to the literature there is no agreement yet about the type of the surgical procedure. But any type of treatment (surgical or other) is mandatory since life expectancy ranges from 2 to 5 months without a relief of obstructive jaundice! (7)

Criteria of resectability are obtained pre-operatively by the triad "cholangiogram + CT and/or MRI + selective angiogram". (6) Radical procedure can be achieved by simple bile duct resection in a few cases. Most of them need also a vascular resection and reconstruction +/- liver resection +/- DHPE in order to be labeled "radical". (19)

Many authors advocate only palliations in EHBDC by pointing the lack of significant differences between the recurrence rates and median survival after radical and palliative operations on the one hand and the early postoperative morbidity and mortality rates after radical resections are dramatically higher than after palliations. (8,11,12)

*Based on our experience we apply an individual approach to every case of EHBDC and make the final decision about the type of the procedure after the intraoperative exploration - inspection, palpation, instrumental (US, cholangiogram, choledochoscopy) and histological investigation. We found significant differences between the late results after radical and palliative procedures in our material (Table 6). That's why we aim to be radical whenever possible but without taking serious risks and paying attention to all the limiting factors such as: (a) locally advanced tumors and/or distant metastases; (b) advanced age (above 70 but this isn't absolute) and poor general condition of the patient (co-existing cardio-vascular, respiratory, hematological and nephrological diseases); (c) severe jaundice - total serum bilirubin > 350 μmol/l.*

How should a palliative procedure be done?

Endoscopic insertion of a biliary stent and interventional radiological procedures (percutaneous external biliary drainage) offer an alternative to conventional surgery. In

the beginning of 1980's endoscopic biliary stenting (EBS) was characterized by high morbidity and mortality rates and short median survival. (9,15) At present EBS is characterized by: (a) successful installation and effectiveness (release of jaundice) in more than 90% of indicated cases; (b) duration of effectiveness - about 3 months for plastic and 6-7 months for metal stents; (c) survival rates comparable to those of surgery, but this type of treatment is much cheaper and the median hospital stay is shorter. (13,17)

In our practice we prefer EBS only in cases of unresectable malignant biliary obstruction detected preoperatively and lack of duodenostasis which indicates gastro-jejunostomy.

Are chemo- and radiation therapy indicated in BDC?

Recently most authors emphasize on the fact that appropriate treatment of EHBDC needs to be multidisciplinary including chemo- and radiationtherapy. (14,16) However there is no enough experience. Most of the reports are on single cases or small series. Though the initial results are promising further studies are necessary for making final conclusions.

## CONCLUSIONS

1. EHBDC is observed more often in patients above 60 years of age, it has aggressive biology and poor prognosis;
2. Reliability of US, ERCP, CT-scan and MRI in cases of EHBDC exceeds 95%. These methods are able to answer the question whether there is or there isn't EHBDC quite satisfactory but they couldn't be used for early diagnosis neither for screening.
3. Most of the patients with EHBDC all over the world as well as in Bulgaria are diagnosed lately - more than 70% in stage III and IV. This determines the low resectability rate and the unsatisfactory late results - postoperative survival of short median duration;
4. EHBDC's of the middle and distal parts are more suitable for radical resections than proximal and total tumors.

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