

## THE MULTIMODAL TREATMENT OF CENTRAL AND PERIPHERAL CHOLANGIOCARCINOMA – ANALYSIS BASED ON A SINGLE CENTER EXPERIENCE

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### Abstract

*The hilar and intrahepatic location represents the most frequent positioning of cholangiocarcinoma. Late diagnosis, tumour resection - as the sole method of radical treatment require a multimodal approach of this form of malignancy.*

**Material and methods.** *The paper is based on a retrospective study conducted on a series of 56 patients diagnosed with hilar and peripheral cholangiocarcinoma admitted and treated in the 3rd Surgical Clinic Cluj-Napoca between September 2004 - December 2010. The series included patients treated with radical or palliative surgical treatment, or patients who underwent minimally invasive treatment of biliary endoscopic or percutaneous drainage followed or not by surgery. We analyzed the data on the postoperative morbidity and mortality, surgical re-interventions, the percentage of patients who received curative resection with radical intention or palliative treatment.*

**Conclusions.** *Cholangiocarcinoma is an aggressive form of cancer and commonly diagnosed late. The cholangiocarcinoma resectability results are comparable to those in literature and may be improved by increasing the number of tumor resections with negative resection margins. The main goal of the palliative procedures is the improvement and remission of the obstructive jaundice, in most cases being successful. The multimodality of the cholangiocarcinoma treatment is a reality, but also a goal in the group of patients studied, the number of patients in which the sequential treatment biliary drainage – surgical treatment were applied being still low.*

**Keywords:** cholangiocarcinoma, surgical treatment, tumoral resection, multimodality.

### Introduction

Cholangiocarcinomas are neoplasms that have as a starting point the biliary epithelium and different location in the biliary tree. The peak of incidence is between the sixth and seventh decade of life, most commonly in males,

the incidence and prevalence increasing in the last years. It is still under debate if this increase in prevalence and incidence of cholangiocarcinoma is real or due to complex diagnostic means currently performed. Depending on tumour location, cholangiocarcinoma may have an intrahepatic distribution (peripheral) and an extrahepatic distribution, which may be in turn hilar and distal [1]. Intrahepatic distribution of cholangiocarcinoma has a

frequency of 5-15% and the hilar one (Klatskin tumour) of 60-70%, the distal location being present in approximately 25% of cases.

Research literature reports a peak of the cholangiocarcinoma incidence between 50 and 70 years, a survival rate at 5 years between 25-40% after R0 resection and 0% without resection. Cholangiocarcinoma malignancy is evidenced by the survival rate of patients with un-resectable tumours between 6 and 12 months, the cholangiocarcinoma prognosis ranging along with the extension, location and resectability of the tumour [2].

The treatment of the hilar and intrahepatic cholangiocarcinoma currently requires a multimodal approach, but nevertheless the only curative treatment of the cancer of the proximal biliary duct is surgical therapy, the only therapeutic approach may report a 5-year survival. Aggressive surgery, mainly based on wide liver resection is the only one associated with R0 resection rate, but requires a laborious preoperative preparation, designed to ensure a sufficient residual parenchyma and normal biological conditions. However, surgery finds its place in the palliative treatment of cholangiocarcinoma, or biliodigestive bypass or the transtumoral drainage, being usual approaches with good results on short and medium term.

**Materials and methods**

This study included 56 patients diagnosed with hilar and intrahepatic cholangiocarcinoma admitted to the 3rd Surgical Clinic Cluj-Napoca for therapy during the period September 2004 - December 2010. Within the series of subjects, 6 patients had intrahepatic localization of the cholangiocarcinoma, and 50 patients had hilar location. The criteria for the inclusion of patients in the study targeted patients undergoing radical or palliative surgical treatment, patients receiving a minimally invasive intervention of endoscopic biliary drainage or percutaneous biliary drainage or surgery that followed a minimally invasive intervention of biliary drainage. The study is retrospective and pursues the therapeutic attitude and multimodality of treatment in hilar and intrahepatic cholangiocarcinoma. The study was based on the analysis of patient files, surgery protocols and discharge records.

The study analyzed non-specific parameters (age, sex), symptoms, risk factors, but stressed the tracking of parameters related to therapy. We have analyzed the operability index, the number of radical surgery or those of a palliative nature, the type of surgery, the number and type of complications, postoperative morbidity and mortality. Also, the study analyzed the average length of hospitalization days and pursued the dynamic evolution of pre- and postoperative biochemical and hematological parameters.

**Results**

Patients included in the study were analyzed

retrospectively. Distribution of patients according to sex and age shows a slight predominance of females in the group of patients with cholangiocarcinoma, and the average age was 62.4 years (Figs. 1, 2).

The present study investigated the symptoms of patients included in the series, establishing the high incidence of the obstructive jaundice syndrome, at the time of admission to the 3rd Surgical Clinic Cluj-Napoca. The high rate of obstructive jaundice is of particular importance

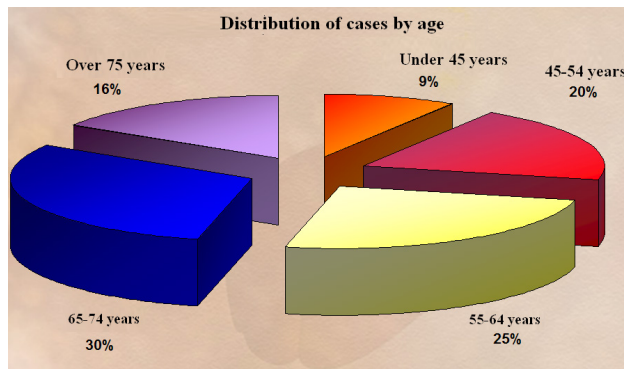


Figure 1. Distribution of cases by age.

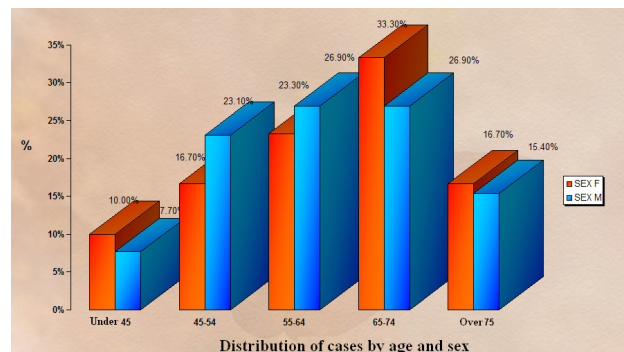


Figure 2. Distribution of cases by age and sex.

in determining the further therapeutic approach because it considers the benefits of a preoperative biliary drainage, to alleviate the suffering of the liver parenchyma in the perspective of a laborious intervention, which may include wide liver resection. In some cases the obstructive jaundice was accompanied by pain localized in the upper abdominal quadrants and fever (Fig. 3), sometimes associated with weight loss but which was not statistically investigated and

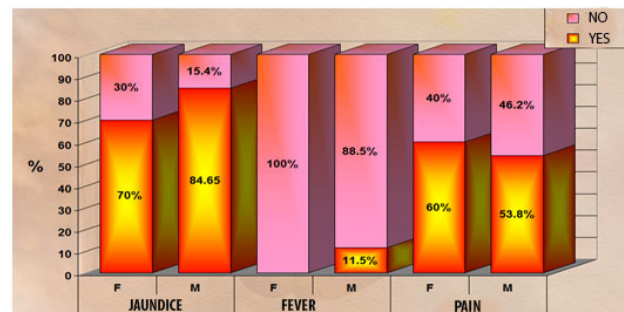


Figure 3. The distribution of symptoms in patients with cholangiocarcinoma included in the study.

which may have a subjective character.

Starting from the principle that the surgical treatment of cholangiocarcinoma is the only one with a curative visa, the present study aims to track the extent to which the surgical approach was used in this type of pathology, what were the results and if other adjuvant treatment methods had been initiated. In the present study we performed surgery on 52 patients in the study group, which represent 92.9% of the subjects investigated; 4 patients were declared inoperable or refused surgery. Of the 52 patients included in the study 28 patients underwent surgery with radical intention (53.8% of the patients operated, 50% of those included in the study), and 24 patients underwent palliative interventions (46.2% of the patients operated).

In some of the patients included in the study it was necessary to perform preoperative biliary drainage. Preoperative biliary drainage was performed either endoscopically (endoscopic retrograde cholangiopancreatography), or through ultrasound-guided percutaneous biliary drainage. Thirteen patients underwent preoperative endoscopic stenting, in order to decrease biliary retention and the remission of hepatocytolysis syndrome, and in 5 patients the preoperative biliary drainage was performed percutaneously. In the case of 2 patients who underwent postoperative percutaneous

**Table 1.** Surgical interventions performed.

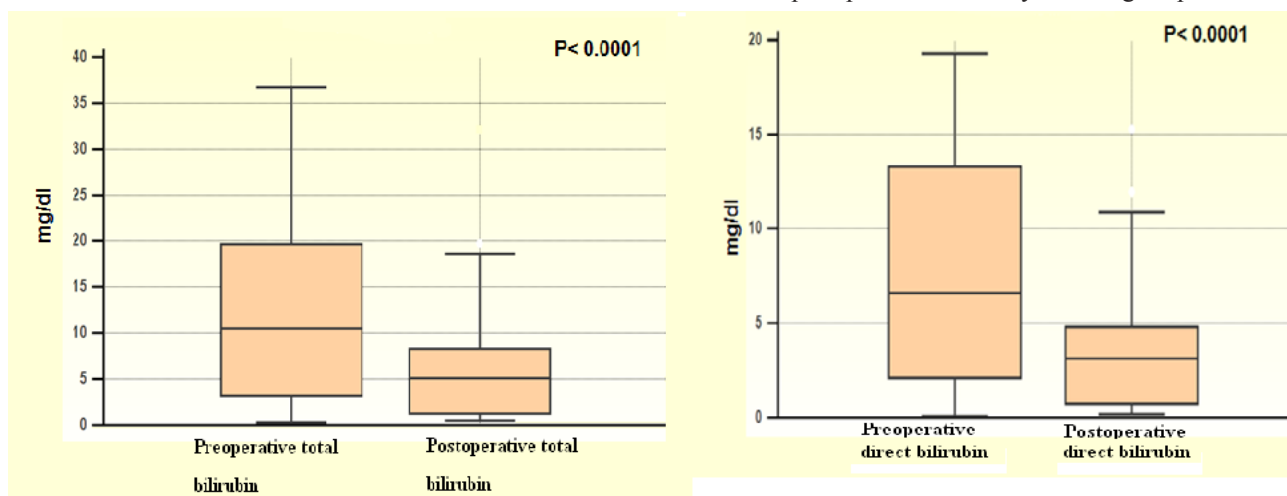
Type of surgical intervention	Number of cases
Biliary resection	16
Right hepatectomy	1
Left hepatectomy	6
Segmental liver resection	4
Atypical liver resection	1
Transtumoral drilling	6
Biliodigestive anastomosis without tumour resection	2
Exploratory laparotomy	12
Other interventions	4

biliary drainage, in one case the endoscopic stenting was performed preoperatively, followed by surgery (exploratory laparotomy) and later on by postoperative percutaneous drainage, because the endoscopic biliary drainage was unsuccessful. The time interval between preoperative biliary drainage and surgery ranged between 4 days and 60 days, with situations where biliary drainage was performed in another medical service, and in these cases we were not able to record the time between biliary drainage and surgery. The endoscopic technique of biliary stenting used mostly plastic stents, which is explained by the high cost and the fact that during the biliary drainage a surgery with a radical character was aimed subsequently.

The radical surgical procedures consisted of liver resections (segmentation, atypical), hepatectomy or main bile duct resection. In two cases of the 6 patients who underwent left hepatectomy a caudate lobe resection was performed, the caudatectomy being part of the standard treatment of hilar cholangiocarcinoma. The palliative surgical procedures were the transtumoral drilling, biliodigestive anastomosis without tumour resection, with a fairly high number of exploratory laparotomy, with tumour biopsy, supplemented by the resolution of the jaundice syndrome by means of endoscopic or percutaneous drainage (Table I). In 4 cases cholecystectomy with subhepatic drainage was performed, ligature of the right portal branch, metastasectomy and transmesocolic gastroenteroanastomosis.

The evolution of the cholestatic enzymes and total and direct bilirubin values marked a dramatic decrease, statistically significant ( $p < 0.0001$ ), and in case of transaminase post-operatively we recorded a slight increase of value, statistically insignificant, which is explained by the recent anesthetic history by the hepatocyte still suffering (TGO preoperative = 134.71 U/l, postoperative = 150.02 U/l; TGP preoperative = 155.8 U/l, postoperative = 197.78 U/l) – average values.

The perioperative mortality or during hospitalization



**Figure 4.** Evolution of total and direct bilirubin values pre- and postoperatively (statistically significant).

in our service was recorded in two cases, namely on the 1<sup>st</sup> day and 3<sup>rd</sup> day postoperatively, death occurring due to disseminated intravascular coagulation and septic shock. The average of hospitalization days was 17.35 given that during hospitalization patients were prepared preoperatively or received preoperative biliary drainage procedures.

A total of eight patients included in the study underwent further surgery (14.28%), in 4 cases re-interventions were due to bleeding complications. In one case there was a cardiovascular complication represented by paroxysmic supraventricular tachycardia treated by the intensive care department. In three cases it was recorded an upper gastrointestinal bleeding externalized by haematemesis or melaena and we treated it conservatively. One patient had choleperitonitis after the suppression of the percutaneous drainage, and in one case a patient had a collection in the gallbladder fossa; in both cases patients were treated conservatively. There was a single case of postoperative right subcostal wound infection solved by daily dressings. There were no pulmonary complications.

Intraoperative blood loss ranged between 200-2300 ml, the maximum blood loss recorded in case of a major hepatic resection and the Pringle maneuver.

There were no cases in which neo-adjuvant oncologic treatment was initiated. We initially applied in all cases surgery or preoperative minimally invasive intervention. The neo-adjuvant oncologic treatment is difficult to implement due to secondary jaundice and alteration of the general condition. In one case we initiated photodynamic therapy, but we recorded no documentation by means of which to judge progress according to this treatment.

### Discussion

This study aimed to describe the main therapeutic strategies of hilar and intrahepatic cholangiocarcinoma in patients who were hospitalized at the 3<sup>rd</sup> Surgical Clinic Cluj-Napoca between September 2004 and December 2010. At the same time it attempts to compare the data obtained with those from the medical literature and discusses the treatment directions requiring improvements of the approach in our department.

Surgical treatment, the only one with a curative visa, is difficult to practice with radical intent due to the late presentation in a specialized service, and due to the low rate of resectability caused by the biological development of this type of neoplasia. The resectability rate of cholangiocarcinoma ranges between 21-60%, depending on tumour stage, the flaws associated with the patient and the surgical team experience. In terms of cholangiocarcinoma resectability, the success rate was 57.89%, which is comparable to the data in literature [3]. The research literature shows a high resectability rate in case of extended liver resection with the association of vascular resections [4], a therapeutic strategy which is at the beginning in the department to which the group of

patients studied belongs.

A specialized centre with experience reports resectability rates of up to 75% given that the rate of major hepatectomy may reach 85% [5]. The prognosis of hilar and intrahepatic cholangiocarcinoma is related to several factors: R0 resection or palliative R1, the achievement of an optimal lymphadenectomy, the degree of vascular invasion, the tumor differentiation degree and the histological type [6]. In the study performed in some cases the presence of the positive or negative resection margin was not specified, having 4 cases in which resection margins were malignantly infiltrated. As a result, it is absolutely necessary to obtain a R0 resection margins to achieve a survival comparable to the research literature. Despite obtaining negative resection margins, the 5-year survival remains low, ranging between 25-40%.

The non-resectability criteria for patients included in the study were represented by the presence of extrahepatic metastasis, peritoneal carcinomatosis, extrahepatic organs invasion, lymph node metastasis N2 with the development of a tumour block, lesion Bismuth IV, portal vein bifurcation embedding or occlusion, invasion of one of the hepatic artery. Currently the research literature no longer considers as a criterion for non-resectability the invasion of one of the hepatic artery and the invasion of the right portal branch, of the portal and partial confluent of the left portal branch respecting the bile duct [7]. They maintain as a criterion for non-resectability the bilateral tumour invasion beyond the second bifurcation, and the presence of extrahepatic metastasis or of peritoneal carcinomatosis. The presence of liver metastases is not fully a non-resectability criterion currently. Depending on their intraparenchymal position the tumor can be considered resectable.

A study published by Ebata et al in 2003 and performed on 160 patients with cholangiocarcinoma who underwent 52 portal resections, appreciated that surgical mortality was similar in patients who underwent resection of the portal vein with that of cases where a hepatectomy without a vascular resection was performed, but that the macroscopic portal invasion adversely affects survival [8].

The golden standard in surgical treatment of hilar and intrahepatic cholangiocarcinoma actually includes the caudate lobe resection which is associated to a liver resection or to a resection of the main bile duct [7]. In the study performed the caudate lobe resection was performed in two cases, according to the strategy generally accepted today.

Exploratory laparotomies had an increased rate in the present study, over 20% in our study, compared to fewer than 10% in studies reported in the literature [9] and that aspect can be corrected through a better preoperative assessment of tumour resectability, or through laparoscopic staging.

Obstructive jaundice is the main clinical manifestation in patients with hilar cholangiocarcinoma,



being present in 90% of cases [10]. Its consequence is represented both by the secondary suffering of the liver parenchyma and by the increased operative risk. It is estimated that the optimal value of preoperative total bilirubin should be less than 7 mg/dl, given that the hilar neoplastic obstruction can increase the total bilirubin to values up to 30 mg/dl. Mechanical jaundice requires a biliary decompression either as palliative treatment or as a first time operation followed by a radical attitude. The variant of the preoperative biliary drainage is appropriate in these circumstances and can be achieved either endoscopically through endoscopic retrograde cholangiopancreatography or by percutaneous biliary drainage. There are many discussions in the research literature regarding the benefits and risks of endoscopic biliary drainage, knowing the degree of secondary angiocholitis of this type of manual labour [11].

The endoscopic drainage triggers interest from the point of view of the type of stent inserted – metallic or plastic, and the opportunity of unilateral or bilateral assembly of the stent. It is accepted as a therapeutic attitude, the mounting of a metal stent in the conditions of a high cost, but with a lower rate of its replacement secondary to non-functionality. It turns out that the bilateral insertion of the stent does not bring significant benefits increasing the risk and aggressiveness of cholangitis, which is why unilateral stenting is preferred [12]. The results of studies in literature highlight the modern sequential approach preoperative biliary drainage - surgery, which reduces surgical risk and improves the quality of the remaining parenchyma [13].

### Conclusions

Analyzing the results of the study we can develop and support the following conclusions:

1. The results of the cholangiocarcinoma resectability are comparable with the research literature, but the need to increase the number of tumour resection with negative resection margins is imperative in order to improve the curative surgical treatment results.
2. The correct preoperative staging and the introduction of laparoscopic staging in order to reduce the number of exploratory laparotomies are directions which must be followed in the treatment of cholangiocarcinoma.
3. The multimodality of cholangiocarcinoma is a reality, but also a goal in the group of patients studied, as the number of subjects in which the sequential treatment biliary drainage – surgery was applied was reduced.
4. The percentage of palliative intervention is comparable to that of the research literature, the main

objective of being represented by biliary drainage.

5. Haemorrhagic complications occurred mainly in patients undergoing surgery with radical intent and represented 50% of the rate of complications requiring surgical re-intervention. The perioperative mortality (n = 2) was mainly due to the extremely serious complications with a reserved prognosis, but a correlation between the complexity of the surgery and the risk of death could not be made. In case of patients undergoing surgical re-interventions no deaths occurred during hospitalization.

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