Survival and Quality of Life of Cholangiocarcinoma Patients: a Prospective Study over a 4 Year Period

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Abstract

Background and aims: Cholangiocarcinomas (CCAs) are tumors with a poor prognosis and a lower quality of life (QoL). The aim of this study was to evaluate the survival rate and quality of life in CCA patients. Method: We prospectively enrolled 133 patients diagnosed with CCA in the 3rd Medical Clinic, Cluj Napoca, over a 4-year period (2005-2009). The QoL was evaluated by means of a QoL questionnaire (EORTC QLQ-C30). Results: The mean age of the patients was 65 ± 10.6 years: 55% were males. 71% of the patients had hilar tumor (Klatskin), 23% distal and 6% intrahepatic CCA (IH). Only 11.3% of the patients were eligible to receive curative treatment. The 1-year overall survival was $22.3 \pm 4.4\%$ and the 2-year survival was $3.4 \pm 2.1\%$. The patients receiving metallic stents had better survival than those receiving plastic stents (40.4% vs 12.5% at 1 year, 9.1% vs 5.0% at 2 years, respectively). The post-therapy QoL demonstrated a less improvement in Klatskin tumor patients than in patients with other types of tumors. Endoscopic palliative therapy allowed a faster community reintegration, but with variable evolution. Conclusions: The highest 2-year survival rate was 5.5%. Slightly longer survival was recorded when chemotherapy was added and also after endoscopic placement of metallic stents. Endoscopic biliary decompression improved the QoL faster than surgery.

Key words

Cholangiocarcinoma – survival – quality of life – biliary stents – adjuvant chemotherapy – curative surgery – TNM stages.

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Introduction

Malignant biliary tract tumors or cholangiocarcinomas (CCAs) are rare tumors, about 3% of all digestive tumors and 10-15% of the hepatobiliary tumors. They have a severe outcome and a poor prognosis. The 5-year survival is about 5% and it depends upon the stage and histological type of the tumor [1].

Cholangiocarcinoma diagnosed at advanced stages can only be treated by palliative surgery or endoscopy. Chemotherapy or radiotherapy have not yielded encouraging results in these patients. The quality of life (QoL) of these patients can be improved through the removal of the biliary obstruction and it is desirable to choose the least invasive method that increases survival besides improving the patient's QoL.

The aim of this study was to assess survival and QoL of patients diagnosed with CCA, in relation to the type of the tumor and therapy.

Patients and methods

We prospectively followed up 133 patients diagnosed with CCA in a tertiary referal center, the 3rd Medical Clinic, Cluj Napoca, between 2005 and 2009. All participants gave written informed consent, and the study was approved by the local Ethics Committee and in accordance with the revised Declaration of Helsinki.

The CCA diagnosis was established through a clinical, biological and imaging examination. The TNM staging was accomplished according to the "American Joint Committee on Cancer Staging" criteria for intra- and extrahepatic CCAs [2]. The treatment was initiated according to the tumor stage (curative or palliative surgical or endoscopic).

The QoL of the patients was assessed by questionnaires filled in at the moment of diagnosis, one month after treatment and afterwards at three-month intervals. The EORTC QLQ-C30 (the European Organisation for Research and Treatment of Cancer QOL questionnaire) validated for Romania [3, 4] includes 30 questions quantifying the patient's status: 15 questions on the emotional, cognitive, physical, social and role functioning; 7 questions on pain,

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fatigue, nausea and vomiting; 2 questions on the global health status and QoL; and 6 independent questions monitoring dyspnea, appetite loss, insomnia, constipation, diarrhea and financial difficulties. The question scores were translated by using mathematical formulas into values ranging from 1-100. In order to quatify the global health status, an overall improvement of QoL was considered a high score. For the other 14 categories, a high symptom level equalled a high score.

Statistical analysis

The survival was analyzed using the Kaplan-Mayer method. Between-group comparisons were performed with the log-rank test. We included in the multivariate logistic regression analysis the type of treatment (metallic stent, plastic stent and palliative resection), the stage of the disease and tumor location. Regarding the QoL questionnaires, the changes in scores over time were analyzed by means of Friedmann Anova and Wilcoxon tests, as required. A 0.05 significance threshold was selected for the p value of all scores. The data were processed using SPSS 17.0 Statistical Package (Chicago, II, USA).

Results

Patients' characteristics

We recruited 133 patients with a mean age of 65 (range 36-85); 123 patients (92%) were over 50 years old. The male/female ratio was 1.2/1. The tumor was located in 71% of cases in the hilum (Klatskin tumors, K), of which 33% were Bismuth IV type [5]; 23% had a distal (DI) and 6% an intrahepatic (IH) location.

Most patients were diagnosed at a late stage: 59.4% in TNM stage IV and 21.8% in stage III. Three patients were not staged due to the brief hospitalization. Only 11.3% of the patients benefited from curative surgery, 25.6% had palliative surgery and 66.9% had endoscopic treatment (Table I)

Table I. Patients' treatment according to the tumor location

No patients	%	Intrahepatic (No)	Hilar (No)	Distal (No)	
15	11.3	3	9	3	
34	25.6	1	23	10	
89	66.9	1	64	24	
78	87.6	1	54	23	
11	12.3	0	10	1	
11	8.3	1	6	4	
22	17.1	4	15	3	
4	3.1	1	1	2	
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Survival

Ninety-one patients were followed over a period of 2 years. The global survival was $22.3 \pm 4.4\%$ at 1 year and 3.4 $\pm 2.1\%$ at 2 years, with a median of 5 months (range 0-24 months) (Fig. 1).

Depending on location, the 1-year survival rate (S1) was 33.3% in patients with IH, followed by those with



Fig 1. Survival rates according to the tumor location (p= 0.891). (______ intrahepatic tumors, ------ hilar tumors, ______ distal tumors)

extrahepatic tumors: 23% for K tumors and 19% for DI tumors (p= 0.813). The highest 2-year survival rate (S2) was observed in patients with DI tumors (4.8%) (p= 0.036) (Fig. 1).

Depending on stage, the 2-year survival was better in stage II tumors as compared to stage III and IV tumors (p= 0.066) (Table II). The mean age of patients in stage II (n= 8) was 63.8 ± 9.8 years; 7 of these patients had a K and 1 patient had a DI tumor. Five patients (61.1%) died in the first 4 months after diagnosis; 2 patients died in the early postoperative period (after curative resection) due to liver failure or other comorbidities (Fig. 2).

Tabel II. Survival of	patients according	to the tumor stage
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	1	0		0
Stage	Patients n=91	S1 %	S2%	Median (months)
II	8	37.5	25	4
III	22	31.8	9.1	5
IV	60	17.1	3.3	5
NA	1	0		

NA, not available

Depending on treatment, the survival rate of patients with palliative resection was 37.5% at 1 year as compared to stented patients - 18.2% (p= 0.856). At 2-years, patients with palliative resection had a 4.2% survival rate as compared to stented patients 5.9% (p= 0.776) (Fig. 3).

We recorded a better 1 and 2-year survival in patients receiving metallic rather than plastic stents, but without statistical significance (40.4% vs 12.5% p= 0.171 at 1 year and 9.1% vs 5.0% p= 0.856 at 2 years respectively). There was no significant difference (p= 0.221) between the survival with the two types of stent used as analyzed for any tumor stage (Table III).

In the multivariate logistic regression analysis only the treatment type proved to be an independent predictive factor. The metallic stent was validated as positive prognostic factor for survival (p=0.03, OR=0.367, 95% CI=0.149-0.908).

Although survival was not significantly influenced by the treatment, it was longer in patients with chemotherapy.



Fig 2. Survival rates according to the tumor stage (p=0.259) (------ stage II, ____ stage IV)

Table III. Survival of patients according to the treatment

Treatment	Patients n=91	S1 %	S2 %	Median (months)
Curative surgery	6	33.3	0	2
Palliative surgery	24	37.5	4.2	5
Stented	51	18.2	5.9	5
plastic stent	40	12.5	5.0	4
metallic stent	11	40.4	9.1	11



Fig 3. Survival rates of patients with stent compared to patients with palliative resection. (p= 0.44) (palliative resection, ---- stent)

Both patients receiving curative surgery plus adjuvant chemotherapy survived at 1 year as opposed to those undergoing only curative surgery (n=4), who survived less than 4 months. Similarly, the patients treated with palliative surgery or stent placement plus chemotherapy had longer S1 than those treated by surgery or stent placement alone (Table IV).

Quality of life

We recorded the changes in the QoL after treatment in 91 patients, having a mean age of 65.4 ± 10.6 years. The global health status varied significantly in time (p= 0.038). A significant improvement was recorded at 6 months after

 Table IV. One year survival (S1) of patients without and with adjuvant chemotherapy

Treatment	No. patients	S1 (%)	Median (months)	р
Stent	43	28.6	10	0.295
Stent + chemotherapy	8	66.7	5	
Palliative surgery	21	14.5	14	
Palliative surgery + chemotherapy	3	37.5	5	0.512

treatment, as opposed to initial values, in the physical parameters, role functioning, social functioning, insomnia and diarrhea (p<0.01). Quality of life indices varied in time. After 9, 12 or 15 months, depending on treatment type or tumor location, the QoL decreased in all groups.

The assessment of cognitive functioning included questions on the concentration capacity and memory loss. Both parameters showed significant improvement in the 3-6 months interval (p<0.04). Emotional functioning, fatigue and financial difficulties worsened in the first 6 months (p<0.01).

Depending on the tumor location, 69 patients belonged to the K group (with Klatskin tumor) and 22 to the DI group (Fig. 4). The patients in the K group showed a global decrease in QoL in the first 3 months. The physical, cognitive and role functioning improved towards the 6-month threshold, while the social functioning improved throughout the entire period, although with certain oscillations. The emotional function deteriorated during the first 9 months. The evaluated symptoms had a trend to improvement, with an oscillating pattern; fatigue and financial difficulties were the only parameters to deteriorate.

The patients in the DI group showed an increase in the QoL during the first 6 months, with improvement in physical, cognitive and role functioning. The social functioning improved in the first 9 months, the physical functioning oscillated and the emotional parameters remained altered throughout the entire period. The other evaluated symptoms improved in the first period (3 months) and then oscillated; fatigue was the only one to increase during the entire period.



Fig 4. Evolution of the quality of life (QoL) global score according to tumor location (the number of patients decreased with time).



Fig 5. Evolution of the quality of life (QoL) global score according to the palliative treatment (the number of patients decreased with time).

We questioned 72 patients in order to assess QoL depending on the treatment, stenting (n=46) versus palliative resection (n=26; of these, 16 patients were later stented) (Fig. 5). The stented patients experienced a global improvement in the QoL status since the first month. The physical, social and role functioning improved in the first 6 months after stenting, the cognitive functioning improved only during the first month while the emotional functioning required 12 months to improve.

The patients with palliative resection experienced a decrease in the global QoL status in the first 6 months, with a subsequent increase. The social and physical functioning improved and the cognitive functioning decreased in the first 6 months, the emotional one had a slower improvement, while the role functioning had a constant increase throughout the entire period.

We found a significant difference between the two groups regarding fatigue, nausea and vomiting: in the stented group, at 1 month after treatment these symptoms decreased significantly as compared to the surgical group. Afterwards, the stented group experienced an oscillating evolution, while in patients with palliative resection the symptoms decreased slowly towards the 9 month threshold and then increased again.

In both groups, pain slightly fluctuated. Insomnia decreased during the first 6 months in the stented patients as opposed to the operated patients, who experienced a short-lasting decrease. The appetite decreased in the first 6 months in the operated group; appetite in the stented patients increased in the first month and then oscillated. The stented patients had improved intestinal transit, while in the operated patients constipation worsened in the first 3 months.

Discussion

Cholangiocarcinoma was diagnosed in most patients after the age of 50 and had a relatively equal gender distribution. The hilar location was the most frequent one (71%), with a high proportion of Bismuth IV type tumors. The location and epidemiological characteristics are consistent with those of other published series [6].

Given the "silent" development of the tumor, the diagnosis is usually established in advanced stages: 60% of our patients were in stage IV at presentation. This accounts for their low survival rates. Intrahepatic tumors had a better 1-year survival, but also a faster evolution with local invasion and dissemination at distance. The IH tumors are known to be aggressive and to have a poor prognosis [7]. All patients having IH tumors were diagnosed in stage IV.

The surgical resection with curative intent is the only treatment option able to remove the tumor [8] and to ensure a higher survival rate; of course, the result depends on the tumor stage, associated conditions [7] and the surgeon's expertise. Some of the patients die with liver failure, sepsis or postoperative complications [9]. Only 11.3 % of our patients were eligible to receive curative treatment. They did not have longer survival rates as compared to those treated palliatively, because of postoperative complications, comorbidities but probably also the surgeon's limited expertise. The patients having survived the critical first 4 months had a survival rate of 21-23 months.

We noted an increase in the 1-year survival in patients having received chemotherapy, regardless of the type of treatment. The increase was significant in the group treated by curative resection (p=0.04), but the small number of patients in the group did not allow to draw firm conclusions. Similar data were recorded in other studies [10,11]. One study performed on 94 patients found a 40.5 vs 24 months survival in patients treated by resection and chemotherapy (n=41), as opposed to patients treated by surgery alone (n=53) [12].

The 2 year survival rate was slightly higher for patients having received endoscopic stenting vs palliative surgical resection. During the last decade, the minimal invasive treatment, aimed at improving survival and QoL, was increasingly preferred [13], although some studies, found no survival differences between the two groups, despite the initial minor advantages in favour of the stented patients [11, 14].

In the multivariate logistic regression analysis, the treatment proved to be an independent predictive factor. The metallic stent was validated as a positive prognostic factor for survival, results consistent with the literature data [15-17].

A higher 2-year survival was recorded in patients having received metallic rather than plastic stents. This may be due to the lower incidence of complications (cholangitis, migration or clogging of the stent) after the placement of metallic stents. In our patients, palliative treatment with either plastic or metallic stents was chosen depending not only on tumor stage, but also on financial issues (costs not covered by health insurance companies). This explained the smaller group of patients with metallic stents and possibly the lack of the statistical significance between groups. The literature data show a significant cost/efficiency benefit of metallic stents when used in patients with longer life expectancy, without liver metastases [17]. Photodynamic therapy (PDT), alone or with stenting, is a new palliative treatment with good results [18-20]. In addition to stenting, PDT significantly improves survival and quality of life in the patients with CCA compared with stenting alone [21]. In our patients, it was performed only in a few cases, so we did not analyze this treatment.

Removal of the biliary obstruction (either surgically or endoscopically) clearly improved the patients' QoL as compared to the initial (diagnosis) moment, which was consistent with other studies [22-25] and decreased after 9, 12 or 15 months depending on treatment or tumor location. Improvement of certain symptoms was obtained thanks to the decrease of cholestasis and the release of bile into the intestine after removal of the obstruction. Interleukins 1 and 6 (IL1, IL6) and tumor necrosis factor α (TNF α) are presumed to be the factors involved in the development of anorexia and appetite loss [26]. Experiments performed on mice with ligated biliary ducts showed an increase in the serum concentration of these citokines and the occurence of anorexia and weight loss [27]. Other studies noted the effect of cholecystokinin (CCK) on appetite. Pancreatic trypsin induces a negative feedback mechanism on CCK [28]; in distal biliary tumors, trypsin does not reach the duodenum, allowing the release of CCK followed by early satiety. After obstruction removal, trypsin reaches the intestine with subsequent improvement of appetite.

Apart from the physical status, the emotional functioning is of major importance in this condition. We found a degradation of the emotional functioning and an increase in fatigue, unlike other studies where patients did not complain of mood variations or depression until 12 weeks after stenting [22].

Patients with hilar tumors had poorer QoL than those with DI tumors and their symptoms improved slower because of impaired drainage of both hepatic lobes. Furthermore, these patients had more frequent posttherapeutic complications: cholecystitis, migration or clogging of the stent [23, 29, 30], postoperative fistulas [31], etc. All these conditions lead to prolonged hospitalization, require analgetic and antiinfectious therapy, limit work productivity and thus the income.

The QoL of our patients improved significantly after treatment for certain periods of time. The improvement of stented patients occurred in the first month but had an inconstant pattern, depending on complications (clogging and migration of the stent). By comparison, the operated patients did not experience major improvement during the first interval, but improvement occurred later.

Studies on CCA patients stented endoscopically showed a rapid and significant improvement with regard to anorexia, dyspepsia, insomnia, diarrhea, physical functioning, role functioning and global status [22-24]. Thus, endoscopic stenting of CCA not only removes jaundice and pruritus, but also provides an increase in the QoL. A study performed on 87 patients, 50 stented and 37 with palliative resection, found no significant differences between the groups regarding survival and QoL, suggesting that the minimal invasive procedure is to be preferred [25]. The palliative treatment ensures an increase in survival and QoL, important for CCA patients in advanced stages. The increase in the QoL and not the prognosis should therefore be the priority.

The QoL studies found a negative correlation between the number of patients included in the study and the extent of time they were followed up; if the follow-up period was longer than 6 months, the results of the study were worse. As the present study was performed on a relatively small number of patients, the results should be viewed accordingly. However, given the low incidence of this condition, it is difficult to gather a larger well-characterized study group. To the best of our knowledge, this is one of the largest survival and QoL studies performed on CCA patients in Europe [22-24].

Conclusions

Our study showed that the diagnosis of biliary tract cancer was in most cases established in advanced stages. The 2-year survival reached only 5.5%, with the longest survival recorded for distal tumors. A slightly longer survival was recorded for stage II patients, after endoscopic placement of metallic instead of plastic stents, and when chemotherapy was associated. The quality of life was improved by therapy, either radical or palliative. Endoscopic palliative treatment allowed a faster community reintegration, as opposed to the palliative surgery, which was followed by improvement only after a longer period of time.

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Conflicts of interest

None to declare.

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