Predictors of outcomes in surgery for hilar cholangiocarcinoma

YU.A. KOVALENKO, YU.O. ZHARIKOV, I.A. KUKEEV, V.A. VISHNEVSKY, A.V. CHZHAO

Vishnevsky National Medical Research Center of Surgery of Healthcare Ministry of Russia, Moscow; Sechenov First Moscow State Medical University of Healthcare Ministry of Russia (Sechenov University), Moscow

Aim. To determine significant predictors of long-term outcomes of surgery for portal cholangiocarcinoma.

Material and methods. Analysis included 49 out of 84 patients who were operated at the Vishnevsky Institute of Surgery in 2003—2016. Morphological examination (2011—2016) revealed great percentage of following positive variables: microvascular (42.9%) and lymphovascular invasion (11.8%), positive resection margin (59.2%), perineural invasion (83.3%), depth of invasion — (83.3%), cells in surrounding fatty tissue (92.3%), invasion of entire thickness of bile ducts’ walls (57.1%). Hemihepatectomy was carried out in 50 (59.5%) cases, advanced hemihepatectomy — in 16 (19%) patients. Left-sided hemihepatectomy (34.6%) was more common compared with right-sided hemihepatectomy (8.6%) for biliary confluence lesion (Bismuth—Corlette type IV).

Results. TNM stage (p=0.29), tumor localization Bismuth—Corlette type (p=0.10), regional lymph nodes metastases (p=0.77) do not significantly affect survival in univariate analysis. At the same time, TNM stage was significant factor if patients dividing into groups was considered (p=0.05). In regression analysis tumor cells differentiation (p=0.00028), positive resection margin (p=0.0034), perineural invasion and depth of invasion (p=0.00086) were significant predictors of survival. Multivariate analysis confirmed prognostic role of lymphovascular invasion alone (p=0.05). There was no correlation between survival and TNM stage (η=0.057), depth of invasion (p=0.229) and lymphovascular invasion (p=–0.143645). There was significant reverse moderate correlation between survival and perineural invasion (η=–0.468750), resection margin (η=–0.558) and tumor differentiation grade (η=–0.481).

Conclusion. Significant predictors of long-term outcomes of surgery for portal cholangiocarcinoma are TNM stage, lymphovascular invasion, tumor cells differentiation, perineural invasion.

Keywords: hilar cholangiocarcinoma, prognostic factors, surgical treatment.

Introduction

Treatment of hilar cholangiocarcinoma (HCC) is one of unsolved problems of surgical hepatology [1]. According to leading world clinics, 5-year survival after advanced liver resections for biliary confluence cancer is 20—60% depending on stage of disease [3, 4].

Over the last decades advanced knowledge about liver and bile ducts anatomy, improved resuscitation and anesthetic measures and surgical technologies have made it possible to expand indications for advanced and combined liver resections. The last is associated with increased percentage of R0-resections and improved long-term outcomes [9, 15]. ‘Aggressive’ surgical approach in HCC patients is accompanied by tumor resectability in 70% of cases and 5-year survival near 60% in some surgical centers [8, 9]. Some reports have also shown that additional resection of liver segment 1 significantly improves survival in HCC patients [13, 14].

At present time it is confirmed that long-term outcomes are also influenced by various clinical and morphological factors besides type of resection [5—7]. There is a correlation of tumor cells differentiation, depth of invasion, perineural and microvascular invasion, as well as distant metastases with survival rate in HCC patients [11, 12].

Some authors also reported resection margin, regional lymph node involvement, tumor differentiation grade and vascular invasion, age, somatic status, TNM stage (T) are independent predictors of survival [10, 11].

However, there is no unified understanding of prognostic factors’ role in HCC patients today [11]. It is caused by small sample sizes and absent comprehensive analysis of tumor’s morphological characteristics regarding long-term outcomes.

The aim of the study was to analyze surgical outcomes in HCC patients considering clinical and morphological characteristics of tumor.

Material and methods

There were 84 patients with hilar cholangiocarcinoma who were treated at the Vishnevsky National Medical Research Center of Surgery in 2003—2016 (table 1). Analysis included 49 patients. Morphological characteristics have been assessed for the period 2011—2016 because high-grade pathomorphological examination was possible in this time.

Hemihepatectomy (HHE) or advanced hemihepatectomy (ahHHE) were predominant. Isolated bile ducts resection was the rarest. In 2003—2010 resection of liver segments 4, 5 followed by ducts resection was carried out.

In case of biliary confluence lesion (Bismuth—Corlette type IV), type of surgery depended on data of urgent intraoperative biopsy of proximal margin of the bile duct and technical possibility of biliodigestive anastomosis creation in some cases. There was a predominant left-sided HHE because tumor cells in left lobar duct were detected in 34% of cases, while in right duct — only in 8.6%.

*e-mail: dr_zharikov@mail.ru
Exclusion criteria were multiple primary cancer, extrahepatic invasion, previous liver and bile ducts surgery without resection, palliative liver and bile ducts resection, no biological characteristics of the tumor, combined hepatobilioangiocellular cancer.

We have analyzed 9 morphological characteristics of tumor which are responsible for tumor progression and associated with certain long-term outcomes according to the literature. Microvascular and lymphovascular invasion was noted in 42.9% and 11.8% of cases respectively, positive resection margin — 59.2%, perineural invasion — 83.3%, complete invasion of bile duct’s wall — 83.3%, cells in surrounding fatty tissue — 92.3%, invasion of entire thickness of the wall and adjacent structures — 57.1%.

These variables were used to assess regional spread of tumor, for pTNM staging and to determine type of resection. In this regard, all factors were divided into two groups depending on tumor’s characteristics: clinical (group 1), morphological (group 2). The first group consisted of TNM stage, localization of tumor (Bismuth—Corlette type) and involvement of regional lymph nodes of gastroduodenal ligament (GDL). The second group covers complete set of histological parameters: differentiation grade, microvascular and lymphovascular invasion, tumor cells within resection margin, liver invasion, perineural invasion, tumor cells in surrounding fatty tissue, depth of bile duct wall invasion, and type of tumor growth.

Relationships of survival and prognostic factors was analyzed using Cox regression model. Correlations were studied using Spearman’s test. Kaplan—Meier survival analysis was performed, curves were compared by using of log-rank test.

### Results

Univariate and multivariate analysis was applied to identify predictors which might be used for prognostic scales, and to determine significant effects. Thus, analysis included 12 factors reflecting tumor spread in patients after liver and bile ducts resection. Relationships between clinical characteristics of tumor and survival are presented in Table 2 (2011—2016).

As you can see in this table, tumor differentiation grade, positive resection margin, perineural invasion and depth of bile duct wall invasion are significant predictors. Bismuth—Corlette type does not reflect spread of tumor process and only determines localization of tumor. At the same time, this factor is important to define type of liver and bile ducts resection. Lesion of regional lymph nodes of hepatoduodenal ligament is also not significant variable.

According to multivariate analysis, only lymphovascular invasion (tumor cells and emboli in lymphatic vessels) is a reliable factor affecting long-term results. At the same time, even tumor differentiation grade was not significant factor ($p=0.07$).
However, patients were divided into three groups for more accurate analysis of stage of disease: group 1 included patients with stage II, group 2 — stages IIIA and IIIB, group 3 — stage IV (fig. 1).

Thus, only stage of disease significantly affects long-term outcomes in this analysis ($p=0.05$).

We have also studied the effect of 9 morphological factors on survival depending on TNM stage and bile duct resection margin. Multivariate analysis was performed depending on presence of tumor cells in bile duct resection margin. Patients were divided into three groups depending on type of resection (table 3).

Thus, only lymphovascular invasion has a significant influence on survival that is confirmed by previous general multivariate analysis.

Comparative analysis regarding positive or negative resection margin also confirmed significant effect of this factor on long-term outcomes ($p=0.00083$) (fig. 2).

Correlation between clinical and morphological factors was studied by using of Spearman’s test. TNM stage and survival as long-term outcome were selected. the Tumor differentiation grade, lymphovascular and perineural invasion, type of resection margin and depth of bile duct wall invasion were selected among histological characteristics.

**Fig. 1.** Survival depending on stage of disease.

**Table 3.** Effect of morphological factors on survival depending on resection margin

<table>
<thead>
<tr>
<th>Factor</th>
<th>Significance, p-value</th>
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<tbody>
<tr>
<td>Tumor differentiation grade</td>
<td>0.41</td>
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<tr>
<td>Microvascular invasion</td>
<td>0.85</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>0.04</td>
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<tr>
<td>Lesion of lymph nodes of GDL</td>
<td>0.24</td>
</tr>
<tr>
<td>Liver invasion</td>
<td>0.61</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>0.20</td>
</tr>
<tr>
<td>Tumor cells in surrounding fatty tissue</td>
<td>0.16</td>
</tr>
<tr>
<td>Depth of bile duct wall invasion</td>
<td>0.47</td>
</tr>
<tr>
<td>Type of tumor growth</td>
<td>0.75</td>
</tr>
</tbody>
</table>
There was no significant correlation between stage of disease and survival (mild correlation, 0.057). Significant correlation between depth of invasion and survival was also absent. Correlation was negative or inverse (−0.229). There was unreliable mild inverse correlation between lymphovascular invasion and survival.

Significant moderate negative association was observed for perineural invasion, tumor differentiation grade, resection margin state and survival (fig. 3, correlation on the example of resection margin).

Discussion

In most of cases, HCC is a small tumor infiltrating bile ducts confluence. Unfortunately, diagnostics of portal cholangiocarcinoma is often late despite slow growth of tumor when vascular invasion and spread through perineural spaces are present [2].

It should be noted that Bismuth—Corlette classification only determines tumor localization rather reflects spread of tumor process. In our sample, we confirm that this classification is not significant predictor of survival.

Comprehensive analysis of morphological features of HCC has shown that metastases occur at advanced stages of disease [2]. S. Song et al reported tumor differentiation grade, depth of adjacent tissues invasion and perineural invasion and distant metastases as significant predictors of survival [8]. At the same time, individual approach is important to determine type of liver resection. There were predominant left- and right-sided HHEs due to prevalence of patients with tumors Bismuth—Corlette types III and IV.

Specialists from the Nagoya University’s clinic (Japan) performed advanced hemihepatectomy in only 7.5—10% of patients with Klatskin tumors and they consider this procedure is not advisable for tumor types IIIb and IV without involvement of liver parenchyma or duct of segment IV [16]. However, it is worth noting that the right-sided trisectionectomy with portal vein resection proposed by prof. P. Neuhaus from the Charite—Virchow clinic (Germany) also has many supporters [17].

M. Nagino et al reported following significant predictors of survival after liver and bile ducts resection: combined resection of portal vein and hepatic artery, blood transfusion, histological characteristics of tumor, lymph nodes metastases and type of resection [16].

According to our data, lesion of lymph nodes of hepatoduodenal ligament does not significantly affect postoperative survival. Apparently, these results may be ex-

Fig. 2. R-value effect on survival.
plained by the fact that only one third of patients have metastases in regional lymph nodes. Multivariate analysis confirmed prognostic role of lymphovascular invasion for survival. Perhaps, this finding is determined by the fact that lymphogenous pathway is predominant for HCC cells dissemination. We also found significant effect of TNM stage on long-term outcomes ($p=0.05$) although there was no reliable correlation with survival.

Thus, tumor differentiation grade, positive resection margin, perineural invasion and depth of invasion are predictors of survival. At the same time, it should be noted that significance of those factors not associated with long-term outcomes could depend on small number of «negative» variables in the sample.

Some authors indicate that tumor differentiation grade is controversial factor. Hasegawa et al. reported similar survival in patients with different grades of tumor differentiation [18], while Saxena et al [19] showed that tumor differentiation is a biological marker of invasive potential, possible metastases and prediction of survival.

Thus, our analysis was able to reveal significant correlations between certain factors of tumor progression and survival. So, it is necessary to review criteria of radical surgery regarding long-term outcomes.

REFERENCES


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