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Long-term results of surgical treatment of intrahepatic cholangiocarcinoma

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ABSTRACT

Objective. To evaluate the long-term outcomes of surgical treatment of intrahepatic cholangiocarcinoma depending tumor dimensions, vascular invasion, lymph node metastases, cellular differentiation and quality of resection.

Material and methods. There were 46 patients with intrahepatic cholangiocellular cancer. Extended hemihepatectomy was made in 14 patients (30.4%), resection of two and three liver segments — in 17 cases (36.9%), standard hemihepatectomy — in 15 patients (32.6%). Liver resection was combined with extrahepatic bile duct resection in 5 (10.9%) patients. Liver resection was followed by biopsy of specimens. Dimension and number of tumors, differentiation grade, resection margin, liver capsule invasion, vascular invasion and regional lymph node metastases were analyzed. Forty-four (95.6%) patients were followed-up in long-term postoperative period. Statistical analysis was performed using Statistica 13.2 (Dell Inc., USA) and IBM SPSS Statistics v.25 (IBM Corp., USA) software package. Survival was analyzed using the Kaplan-Meier method. Overall 1-, 3- and 5-year survival rates with two-sided 95% confidence intervals (95% CI) were calculated using IBM SPSS Statistics v.25 software.

Results. Median survival was 37 months, 1-year — 75.9% (60.9-90.9%), 3-year — 57.6% (35.5-79.6%), 5-year — 36% (8.2-63.7%). Median survival after R1 resection was 37 months, R2 resection — 12 months. Median survival was not achieved in R0 group. We found significant differences in overall survival depending on quality of resection. Tumor dimension over 5 cm, low-grade adenocarcinoma, microvascular invasion and lymph node metastases were associated with impaired postoperative survival. However, differences were not significant.

Conclusion. The main surgical strategy in patients with intrahepatic cholangiocarcinoma should be ensuring microscopically negative resection margin.

Keywords: *intrahepatic cholangiocellular carcinoma, surgical treatment, radical surgery, long-term results.*

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Intrahepatic cholangiocarcinoma is the second common primary liver malignancy and characterized by aggressive course. This tumor originates from the bile duct epithelium and is characterized mainly by mass-forming type of growth (other types of growth are less common) [1, 2]. Intrahepatic cholangiocarcinoma accounts for approximately 15% of all primary liver tumors. Moreover, intrahepatic cholangiocarcinoma accounts 10–20% of all forms of cholangiocellular carcinoma [3]. There has been a tendency to increased incidence of precisely this form of cholangiocellular carcinoma in the last decade [1]. At the same time, intrahepatic cholangiocarcinoma is more aggressive due to its biological characteristics compared with other forms of cholangiocellular carcinoma. Moreover, intrahepatic cholangiocarcinoma is usually diagnosed at the late stages, when the tumor is unresectable [4]. Surgical treatment is possible only in 15-20% of patients with intrahepatic cholangiocarcinoma de novo by the moment of diagnosis. This is associated with mild symptoms at the early stages of disease and late appeal for medical care [1, 3].

The problem of cholangiocellular cancer is of particular interest due to unsatisfactory outcomes and poor postoperative survival besides increased incidence of disease. According to various authors, overall 5-year survival usually does not exceed 20-40% even after R0-resection [5]. Neoadjuvant chemoradiotherapy is not proven to be effective. Therefore, surgical treatment is the only preferable to improve survival [6, 7]. However, various factors including tumor dimensions, quality of resection (negative resection margin), regional lymph node metastases, micro- and macrovascular invasion can influence the outcome of surgical treatment [8]. Long-term results of surgical treatment of intrahepatic cholangiocarcinoma are poorly presented in national literature.

The purpose of this study was to evaluate the long-term outcomes of surgical treatment of intrahepatic cholangiocarcinoma depending tumor dimensions, vascular invasion, lymph node metastases, cellular differentiation and quality of resection.

Material and methods

There were 56 patients with intrahepatic cholangiocellular cancer for the period 2011 – 2019 including 19 men (34%) and 37 women (66%). Age of patients ranged from 36 to 82 years (mean 60.4 years). Surgical treatment was performed in 46 (82.1%) cases. Advanced hemihepatectomy was made in 14 patients (30.4%), resection of two and three liver segments - in 17 cases (36.9%), standard hemihepatectomy - in 15 patients (32.6%). Liver resection was combined with extrahepatic bile duct resection in 5 (10.9%) patients. One (2.2%) patient died in early postoperative period from acute liver failure. This patient was excluded from the analysis. Liver resection was followed by biopsy of specimens. Dimension and number of tumors, differentiation grade, resection margin, liver capsule invasion, vascular invasion and regional lymph node metastases were analyzed. Resection was not performed in some cases due to local tumor spread (10 out of 56 patients). These patients underwent transarterial chemoembolization (n=3, 5.3%), radiofrequency ablation (n=2, 3.6%), transarterial chemoembolization and radiofrequency ablation (n=1, 1.8%), tumor biopsy for subsequent chemotherapy (n=4, 7.1%). These patients were excluded from the analysis.

Patients were distributed as follows depending on tumor stage (UICC, 8th edition, 2017): stage Ia - 1 (2.1%) patient, stage Ib - 8 (17.4%) patients, stage II - 11 (23.9%) cases, stage IIIa - 15 (32.6%) cases, stage IIIb - 9 (19.6%) patients, stage IV - 2 (4.3%) patients.

Mean length of hospital-stay was 23 days. Patients were discharged from the hospital for subsequent follow-up as soon as their condition was stabilized. Adjuvant chemotherapy was performed in 39 patients (88.6%). Chemotherapy was carried out using combination of platinum-based (cisplatin, oxaliplatin) and pyrimidine-based (gemcitabine, capecitabine) drugs. Neoadjuvant chemotherapy was performed in one patient (2.2%). Forty-four (95.6%) patients were followed-up in long-term postoperative period.

Statistical analysis was performed using Statistica 13.2 (Dell inc., USA) and IBM SPSS Statistics v. 25 (IBM corp., USA) software package. Median and quartiles were calculated to analyze age of patients. Absolute and relative frequencies were applied for analysis of gender distribution. Survival was analyzed using the Kaplan-Meier method. Overall 1-, 3- and 5-year survival rates with two-sided 95% confidence intervals (95% CI) were calculated using IBM SPSS Statistics v. 25 software. Predictors of survival were determined by using of Cox-Mantel and Breslow tests. Differences were significant at p-value <0.05.

Results

Lesion of one lobe was observed in 33 (71.7%) cases, invasion of both lobes was found in 13 patients (28.3%).

***Table* 1. Characteristics of tumors and types of surgeries.**

Characteristics of tumors	*n*= 46
Tumor < 5 cm	10 (21,7%)
Tumor > 5 cm	36 (78,3%)
Capsular invasion	25 (54,3%)
Vascular invasion	25 (54,3%)
Perineural invasion	16 (34,8%)
Preoperative biliary decompression	7 (15,2%)
CA 19-9	16 (34,8%)
Localization of tumor	
Right lobe	16 (34,8%)
Left lobe	17 (36,9%)
Lesion of both lobes	13 (28,3%)
Differentiation grade	
G2 (moderately differentiated adenocarcinoma)	24 (52,2%)
G3 (low-grade adenocarcinoma)	16 (34,8%)
Type of liver resection	
Bisegmentectomy	10 (21,7%)
Resection of three segments	7 (15,2%)
Hemihepatectomy	15 (32,6%)
Extended hemihepatectomy	14 (30,4%)
Various resections + resection of extrahepatic bile ducts	5 (10,9%)
Quality of resection	
R0 (tumor resection within intact tissues)	14 (30,4%)
R1 (tumor resection along its edge)	17 (36,9%)
R2 (partial resection)	5 (10,9%)

Mean tumor dimension was 8.8 cm (range 2.5–14.0 cm). Solid tumors prevailed (n = 39, 84.8%). Dissemination foci were identified in 5 cases (15.2%). Mass-forming type of tumor growth was detected in the vast majority of cases (n = 43; 93.5%), periductal infiltration – in 3 cases (6.5%). Lymph node metastases were diagnosed in 10 patients (21.7%). Moderate (G2) and low differentiation (G3) of adenocarcinoma was observed (n = 24; 52.2% and n = 16; 34.8%, respectively). Highly differentiated adenocarcinoma was absent in our sample. Liver capsule invasion was found in 25 (54.3%) patients, microvascular invasion - in 25 cases (54.3%), perineural invasion - in 16 cases (34.8%). Preoperative biliary decompression was required in 7 (15.2%) patients. Characteristics of tumors and types of surgeries are shown in **Table 1**. Demographic characteristics of patients and types of surgeries included in the analysis are shown in **Table 2**. Median values and quartiles (Me [LQ; UQ]) are given for age, absolute and relative frequencies - for gender. Overall postoperative survival throughout the entire follow-up period is shown in **Fig. 1**. Median survival was 37 months, 1-year - 75.9% (60.9 - 90.9), 3-year - 57.6% (35.5 - 79.6), 5-year – 36% (8.2 - 63.7).

Analysis of the influence of tumor dimension, differentiation grade, microvascular invasion, regional lymph node metastases and quality of resection on the overall survival is presented in **Table 3**.

Tumor dimension over 5 cm, low-grade adenocarcinoma, microvascular invasion and lymph node metasta-

***Table* 2. Demographic characteristics of patients and types of surgeries.**

	Type of surgery			All patients (*n*=46)
	Bisegmentectomy (*n*=10)	Resection of three segments (*n*=7)	Hemihepatectomy (*n*=29)	
Age, years	60 [52; 64]	61 [58; 69]	61 [49; 68]	61 [55; 68]
Gender, m/f	3/5 (37,5% / 62,5%)	2/5 (28,6% /71,4%)	7/21 (25% / 75%)	13/31 (29,5%/ 70,5%)

***Table* 3. Kaplan-Meier 1-, 3- and 5-year survival depending on various factors.**

	Groups of patients	1-year survival	3-year survival	5-year survival	p-value
Tumor dimension	<5 cm (*n*=10)	88,9 (68,4 - 100) %	All cases censored	All cases censored	P=0,377
	> 5 cm (*n*=34)	72,9 (55,4 - 90,3) %	53,9 (31,1 - 76,8) %	33,7 (7 - 60,4) %	
Differentiation grade	G2 (*n*=24)	77,2 (52,9 - 100) %	66,2 (37,3 - 95) %	66,2 (37,3 - 95) %	P=0,319
	G3 (*n*=16)	62,6 (35,5 - 89,8) %	47 (13,5 - 80,4) %	31,3 (0 - 64,9) %	
Microvascular invasion	Есть (*n*=23)	79,5 (58,6 - 100) %	44,7 (11,6 - 77,9) %	29,8 (0 - 62,4) %	P=0,72
	Нет (*n*=16)	81,4 (64,9 - 97,9) %	48,8 (7,3 - 90,4) %	48,8 (7,3 - 90,4) %	
Regional lymph node metastases	N0 (*n*=17)	88,2 (72,9 - 100) %	88,2 (72,9 - 100) %	All cases censored	P=0,144
	N1 (*n*=10)	80 (44,9 - 100) %	53,3 (4,7 - 100) %	0 (0 - 0) %	
Quality of resection	R0 (*n*=14)	100 (100 - 100) %	80 (44,9 - 100) %	All cases censored	P=0,049
	R1 (*n*=17)	60,6 (33,5 - 87,7) %	60,6 (33,5 - 87,7) %	30,3 (0 - 74,4) %	
	R2 (*n*=5)	0 (0 - 0) %	–	–	

Note: G2 - moderately differentiated adenocarcinoma, G3 - low-grade adenocarcinoma, N0 – no regional lymph node metastases, N1 - regional lymph node metastases, R0 - tumor resection within intact tissues, R1 - tumor resection along its edge, R2 - partial resection.

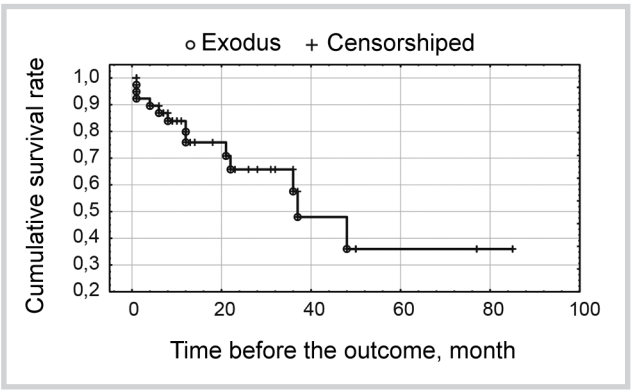

***Fig. 1.* Overall postoperative survival.**

ses were associated with impaired postoperative survival. However, differences were not significant. At the same time, we found significant differences in overall survival depending on quality of resection. The Breslow test as more sensitive to differences within the initial segments of the curves confirmed significant differences **(Fig. 2)**. Median survival after R1 resection was 37 months, R2 resection - 12 months. Median survival was not achieved in R0 group.

Discussion

Currently, the only effective treatment of intrahepatic cholangiocarcinoma is liver resection ensuring improvement of survival. However, this cancer is diagnosed at the late stages in most cases. Approximately 75% of patients require hemihepatectomy or extended hemihepatectomy among those with resectable tumors [9, 10, 11].

Overall postoperative 5-year survival rate is 21-59% **(Table 4)** [9, 12-18].

A large-scale SEER trial showed better survival after radical surgical treatment. However, 5-year postoperative survival is still low [19]. According to our data, overall 1-year survival was 75.9% (60.9 - 90.9), 3-year - 57.6% (35.5 - 79.6), 5-year – 36% (8.2 - 63.7).

In our study, long-term postoperative survival in patients with intrahepatic cholangiocarcinoma was analyzed depending on various prognostic factors including tumor dimension, differentiation grade, microvascular invasion, regional lymph node metastases and quality of resection (resection margin status).

Above-mentioned predictors determine prognosis and spread of the tumor in accordance with the 8th edition of UICC classification (2017). TNM classification of International Joint-Committee on Cancer (7th edition, 2011)

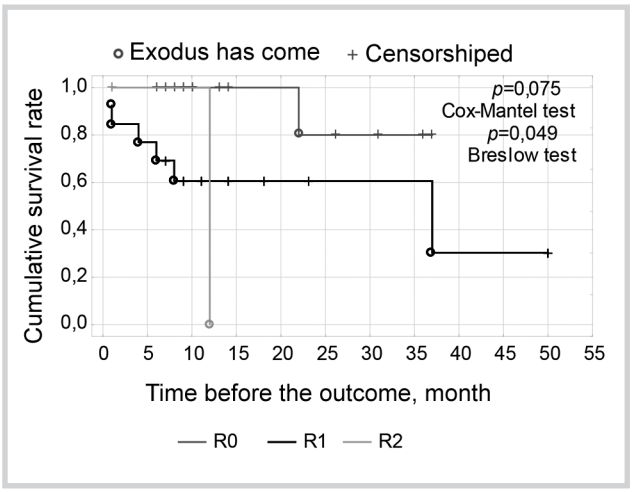

***Fig*. 2. Postoperative survival depending on quality of resection. R0 - tumor resection within intact tissues; R1 - tumor resection along its edge; R2 - partial resection.**

has been previously used for intrahepatic bile duct cancer. The following parameters were evaluated: the number of tumor nodes, vascular invasion, direct invasion into extrahepatic structures, periductal invasion, regional lymph node and distant metastases. However, American Joint-Committee on Cancer (AJCC) revised this classification and published its 8th edition in 2017 [20]. Periductal invasion was excluded from classification in the 8th edition as prognostic factor. At the same time, tumor dimension was accepted as a new parameter (over or less than 5 cm). We analyzed this criterion too.

According to various trials, tumor dimension is a significant predictor of postoperative survival in patients with intrahepatic cholangiocarcinoma. Mavros M.N. et al. (2014) reported tumor dimension as significant predictor of survival [11]. Doussot A. et al. (2016) found that tumor > 5 cm is associated with worse prognosis of survival [21]. However, this parameter did not significantly affect the outcome in other researches [22]. We did not find significant differences in survival of patients with tumor > 5 cm and <5 cm.

Another important predictor of treatment outcome is microvascular invasion. The latest edition of TNM classification considers vascular invasion as a parameter for intrahepatic cholangiocarcinoma staging without specifying micro- or macro-vascular lesion [23]. The effect of microvascular invasion on long-term survival is poorly understood and controversial. Rodríguez - Perálvarez M. (2013) considers that tumor emboli in small vessels result intrahepatic recurrence or systemic metastases [24.]

Shao C. (2017) reported that microvascular invasion is a poor prognostic factor after liver resection in patients with intrahepatic cholangiocarcinoma [25]. In a recent multiple-center study, microvascular invasion was significantly associated with recurrence of intrahepatic cholangiocarcinoma. However, there was no evidence of negative effect on long-term survival [26]. According to our data, survival was similar in patients with and without microvascular invasion.

We also evaluated the presence of regional lymph node metastases. Lymph node metastases is perhaps the most important risk factor for poor postoperative outcome. The prognosis is poor in patients with lymph node metastases even if resection margin is negative (R0) [27]. However, we did not reveal significant correlation of lymph node metastases and survival. It should be noted that survival rate was higher in patients without lymph node metastases in our sample. The lack of reliability is probably due to small sample size.

In general, the current approach to lymphadenectomy is of interest. Some authors reported reduced risk of local and regional recurrence after lymph node dissection. However, prospective studies have not shown any survival benefits associated with lymphadenectomy [28]. On the other hand, lymphadenectomy has prognostic value and improves staging of intrahepatic cholangiocarcinoma. Therefore, this procedure is recommended [29].

Negative resection margin is also one of the most important predictors of prognosis and survival (R0-resection). Thus, a large multiple-center study (2012) showed that R0 liver resection is significantly associated with improved postoperative survival while the distance to resection margin is not a significant prognostic factor [7].

Another authors reported that R1 resection is a predictor of poor survival [30]. According to various data, R0 resection is associated with improved overall 5-year sur-

***Table* 4. Postoperative 5-year survival in patients with intrahepatic cholangiocercinoma.**

Author	Year	Number of patients, *n*	R0,%	5-year survival,%
DeOliveira M.L. et al .	2007	44	45	40
Choi S.B. et al.	2009	64	86	40
Lang H. et al.	2009	83	64	21
Murakami Y. et al.	2011	21	62	37
de Jong M.C. et al.	2011	449	81	31
Ribero D. et al.	2012	434	85	33
Doussot A. et al.	2015	188	–	59
Tabrizian P. et al.	2015	82	–	25
Patyutko Yu.I. et al.	2015	95	–	25
Vishnevsky Institute of Surgery	2019	44	30	36

vival. However, sufficient future remnant liver volume should be a prerequisite after liver resection [7].

We observed significant differences in overall survival after R0, R1 and R2 liver resection (Breslow test, $p<0.05$). None of the patients lived for more than 12 months after R2 resection. Five-year survival after R1 surgery was 30%. One patient died in the R0 group within the follow-up period. However, there was a large number of censored cases in this group and these patients are still under follow-up.

In our sample, tumor dimension > 5 cm, differentiation grade, lymph node metastases and vascular invasion were associated with reduced 3- and 5-year survival. However, no significant differences were obtained despite the use of more sensitive statistical tests (Cox-Mantel, Breslow). Possible cause of the absence of significant differences is a large number of censored cases.

Thus, the main surgical strategy in patients with intrahepatic cholangiocarcinoma should be ensuring microscopically negative resection margin. However, this is often difficult to achieve due to biological characteristics of tumor.

Aggressive surgical approach (R0-resection) should be preferred considering unsatisfactory surgical outcomes in patients with intrahepatic cholangiocarcinoma. Combination of standard and extended surgeries with radio- and chemotherapy is advisable for resectable intrahepatic cholangiocarcinoma.

No conflict of interests to declare.

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