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GUIDELINES FOR CLINICAL PRACTICE

Surgery and chemotherapy for intrahepatic cholangiocarcinoma

Zenichi Morise, Atsushi Sugioka, Takamasa Tokoro, Yoshinao Tanahashi, Yasuhiro Okabe, Tadashi Kagawa, Chinatsu Takeura

Zenichi Morise, Atsushi Sugioka, Takamasa Tokoro, Yoshinao Tanahashi, Yasuhiro Okabe, Tadashi Kagawa, Chinatsu Takeura, Department of Surgery, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsu-kake-cho, Toyoake, Aichi 470-1192, Japan

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Correspondence to: Zenichi Morise, MD, PhD, Department of Surgery, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukakecho, Toyoake, Aichi 470-1192, Japan. zmorise@aol.com

Telephone: +81-562-939248 Fax: +81-562-937060

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Abstract

Cholangiocarcinoma, arising from bile duct epithelium, is categorized into intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC), including hilarcholangiocarcinoma. Recently, there has been a worldwide increase in the incidence and mortality from ICC. Complete surgical resection is the only approach to cure the patients with ICC. However, locoregional extension of these tumors is usually advanced with intrahepatic and lymph-node metastases at the time of diagnosis. Resectability rates are quite low and variable (18%-70%). The five-year survival rate after surgical resection was reported to be 20%-40%. Median survival time after ICC resection was 12-37.4 mo. Only a small number of ICC cases, accompanied with ECC, gall bladder carcinoma, and ampullary carcinoma, have been reported in the studies of chemotherapy due to the rarity of the disease. However, in some reports, significant anti-cancer effects were achieved with a response rate of up to 40% and a median survival of one year. Although recurrence rate after hepatectomy is high for the patients with ICC, the residual liver and the lung are the main sites of recurrence after tentative curative surgical resection. Several patients in our study had a long-term survival with repeated surgery and chemotherapy. Repeated surgery, combined with new effective regimens of chemotherapy, could benefit the survival of ICC patients.

Key words: Intrahepatic cholangiocarcinoma; Surgery; Chemotherapy

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INTRODUCTION

Cholangiocarcinoma, arising from bile duct epithelium, is categorized into intrahepatic cholangiocarcinoma (ICC) and extrahepatic (ECC), including hilar cholangiocarcinoma. ICC, more than 90% of which is adenocarcinoma[1], is the second most, but relatively rare, common primary liver cancer after hepatocellular carcinoma, accounting for 5%-10% of the primary malignancies of the liver[2,3]. Recently, there has been a

Table 1 Recent reported series of hepatectomy for intrahepatic cholangiocarcinoma

Authors	Year	No	Survival rate (%) and MST				Significant prognostic factors for survival
			1-yr	3-yr	5-yr	MST (mo)	
Okabayashi	2001	60	68	35	29	19.6	Number of nodules, lymph-node involvement, vascular invasion, symptomatic tumor
Chen	1999	48	35.5	20.5	16.5[1]		
			27.2	8.8	7.8[2]		
DeOliveira	2007	44			40	28	Surgical margin
Palik	2008	97	74.9	51.8	31.1		Number of nodules, surgical margin
Inoue	2000	52	63	36	36	18	Surgical margin, lymph-node involvements, vascular invasion
Valverde	1999	30	86	22	22	28	Number of nodules, lymph-node involvements
Madariaga	1998	34	67	40	35	19	Number of nodules, surgical margin
Shimada	2007	94	69.5	35.5	31.1	24	Number of nodules, surgical margin, lymph-node involvements
Weber	2001	33		55	31	37.4	Vascular invasion

[1]Data from intrahepatic cholangiocarcinoma patients with hepatolithiasis; [2]Data from intrahepatic cholangiocarcinoma patients without hepatolithiasis; MST: Median survival time.

worldwide increase in the incidence and mortality from ICC, although the incidence and mortality from ECC are decreasing[4,5]. There has also been an increasing number of reports on the surgical treatment of ICC. Complete (R0) surgical resection is the only therapy for the cure of ICC patients. However, the resectability rate is still low and the prognosis following hepatectomy is poor, because the locoregional extension of these tumors is usually advanced with intrahepatic and lymph-node metastases at the time of diagnosis[6]. Although only a small number of ICC cases, accompanied with also ECC, gall bladder carcinoma, and ampullary carcinoma, have been reported in the studies of chemotherapy due to the rarity of the disease,several reports have demonstrated significant anti-cancer responses for ICC using new agents[7,8]. Recently, the treatment strategy for colorectal carcinoma (also adenocarcinoma) has been dramatically altered in the combination of surgery and chemotherapy with new anti-cancer agents, such as CPT-11 and oxaliplatin[9,10]. There is a need of considerations to improve the therapeutic approaches for ICC. It has been reported that ICC may include two pathologically and biologically different types of tumors, peripheral mass-forming (usually hepatitis-based) tumor and central periductal-infiltrating tumor without hepatitis[11,12].

In this article, the outcomes of the treatment with surgery and chemotherapy for ICC patients are reviewed and future prospects are discussed.

SURGICAL RESECTION

Currently, surgical resection of the involved liver segments is the only curative treatment for ICC. However, resectability rates have been quite low and variable (18%-70%), as most patients present at an advanced stage. Surgery has been successful in several reported series, with a 1-year survival rate of 35%-86%, 3-year survival of 20%-52%, and 5-year survival of 20%-40%. In our institute, 44 patients with ICC underwent hepatectomy by 2006 and their 3-, 5- and 10-year survival rates after the first hepatectomy were 51%, 29% and 22%, respectively. Disease-free survival at 5 years varied significantly -between 2% and 41%. Median survival after ICC resection was 12-37.4 mo[11,13-26]. Some of these studies report that peri-operative mortality was less than 5%, which is recently decreasing[11,12,15] (Table 1).

Since there is a limited number of patients in most reports of ICC cases few studies have specifically addressed surgical resection outcomes compared with non-operative treatment. Based on the available studies, surgery should be performed in patients with potentially resectable ICC regardless of its stage. DeOliveira *et al*[15] emphasized the importance of performing a complete resection because the 5-year survival rate among their 44 patients was 63% and the median survival was 80 mo in patients who could achieve an R0 resection. Nakeeb *et al*[18] demonstrated that resection was beneficial; and the 5-year survival was 44% and median survival was 26 mo in those who underwent resection versus 0% and 7 mo, respectively, in patients without surgical resections.

Indicators of poor prognosis noted in two or more studies included positive lymph nodes, positive margins, multiple nodules, vascular invasion, and large tumor size. Other indicators included capsular invasion, histological type, tumor spreading type, bilobar disease, mucobilia, left side involvement, and high CA 19-9[11,14,16,17,21-24]. Chen *et al*[14] also reported that patients with hepatolithiasis had higher rates of resection, and higher incidence of papillary tumors and postoperative complications, but no difference in survival was noted when compared with patients without hepatolithiasis. In a study of 33 patients, the recurrence rate was 61% at 12.4 mo. Liver was the most common site of recurrence, followed by the lung, lymph nodes, and bone[24,25].

In summary, surgical resection of the liver is the only curative treatment with a 5-year survival rate of around 30% and a median overall survival of 2-3 years for ICC patients. Strong prognostic factors after hepatectomy are number of nodules, surgical margin, and lymph-node involvement. Thus, further investigations should be carried out about the treatment for the recurrence after surgery and for patients with factors indicating poor prognosis.

CHEMOTHERAPY

There are not so much evidences for the evidence-based evaluation of the chemotherapeutic efficacy for ICC patients. Only a small number of ICC cases , accompanied with extrahepatic cholangiocarcinoma, gall bladder carcinoma, and ampullary carcinoma, have been reported due to the rarity of the disease. There are also a variety of factors, which influence the effect of chemotherapy and complicate the evaluation, such as control of cholangitis, liver function and performance status, except for tumor-related factors. In this article, studies in biliary tract carcinoma, including ICC, are reviewed.

To date, only two small randomized controlled trials have been published for biliary tract carcinoma[27,28]. An randomized controlled trial on chemotherapy and supportive treatment was conducted in patients with unresectable biliary tract cancer and pancreas cancer[30]. In this study, fluorouracil (5-FU) + leucovorin or 5-FU + leucovorin + etoposide were used for chemotherapy. For all the patients, significantly prolonged survival was observed in the group with chemotherapy [median survival time (MST), 6.0 mo] compared with the group with supportive treatment alone (MST, 2.5 mo). However, due to the small number of patients with biliary tract cancer (37), no significant difference was found between the groups (chemotherapy group MST, 6.5 mo; supportive treatment group 2.5 mo; $P = 0.1$). The rate of improvement in quality of life was also examined in this trial, and a significant difference was found in the chemotherapy group compared with the supportive treatment group (36% *vs* 10%; $P < 0.01$).

The single use of fluoropyrimidines such as 5-FU, or a combination of 5-FU with interferon, leucovorin, or hydroxyurea as biochemical modulators, was often used for advanced biliary tract cancer[27,29-34]. The response rates ranged from 7% to 34% and MST ranged from 6 to 14.8 mo with the combined use of 5-FU and these modulators. However, no difference was observed in survivals of patients with chemotherapy including 5-FU for unresectable biliary tract cancer and patients who received best supportive care.

Since 1999, clinical trials have been conducted with gemcitabine[35-41]. Although methods of administration are varied, relatively good results are reported. The response rates ranged from 0% to 36% and MST ranged from 4.6 to 14.0 mo. Toxicity-induced myelosuppression, such as leucopenia, as well as nausea and anorexia, was mainly observed, although they were well tolerable.

A clinical trial of tegafur/gimeracil/oteracil potassium (S-1), which is an oral anti-cancer drug consisting of tegafur as a prodrug of 5-FU, 5-chloro-2, 4 dihydroxypyridine and potassium oxonate, was conducted in Japan[42,43]. In a late phase Ⅱ trial, a favorable result was reported, with a response rate of 35% and MST of 9.4 mo in 40 patients.

Some reports used mitomycin C, cisplatin, taxanes, and irinotecan (CPT-11)[44-46], which showed a response rate of around 10% and MST of 4.5-6.1 mo.

For biliary tract cancer, since the chemotherapeutic effects are limited with a single agent, many modalities of combined chemotherapy have been carried out[47-65]. Compared with single-agent chemotherapy, the response rate of combined chemotherapy is generally high and the survival period is also inclined to be long. Although a regimen of combined 5-FU, anthracycline and platinum has often been employed, no standard regimen has been established. An attempt at a regimen focusing on the use of gemcitabine is currently being made and a favorable result has been achieved, with the response rate of 28%-38% and MST of 4.6-11.0 mo in patients treated with gemcitabine + cisplatin[66-69].

Therapeutic drugs targeting molecular biological characteristics (molecular targeting therapy) are now also under development. In view of a report suggesting the strong expression of epithelial growth factor receptor (EGFR) in biliary tract cancer, a phase Ⅱ trial using erlotinib, an EGFR-inhibiting drug, is being carried out (response rate 8% and MST 7.5 mo)[70] (Table 2).

In summary, recent advancement facilitates the chemotherapy to achieved a response rate of around-30% and a median survival of more than one year for ICC patients. Key drugs currently available for the therapy are gemcitabine, fluoropyrimidines, and platinums. Further investigations are required for the development of new agents, such as molecular-targeting drugs, and combined therapy with surgery.

POSSIBLE SUBTYPES OF ICC AND THEIR CHARACTERISTICS

Two studies categorized the ICC into subtypes and compared their prognoses. Shimada *et al*[11] categorized ICC into two types according to the classification of the Liver Cancer Study Group of Japan[71]: Mass-forming and mass-forming periductal-infiltrating types, which occurs with a definitive mass but also causes infiltration along the portal pedicle and bile ducts. The mass-forming periductal-infiltrating type was associated more with jaundice, bile duct invasion, portal invasion, lymph node involvement, and positive surgical margins. In their study of 74 patients, those with mass-forming ICC had less local recurrence (76.1% *vs* 92.9%) and a significantly higher median survival (32 *vs* 22 mo) than those with mass-forming periductal-infiltrating ICC. Aishima *et al*[12] classified 87 patients into hilar ICC and peripheral ICC and noted that hilar ICC was more likely to be associated with perineural invasion, lymph node metastases, and extrahepatic recurrence. 1-, 3-, and 5-year survival rates of the peripheral ICC patients were 88%, 72% and 60% compared with 66%, 41% and 36%, respectively, in the hilar ICC patients. The incidence of ICC has increased steadily over the past few decades and viral hepatitis, chronic liver disease, and fatty liver disease have been identified as possible contributing factors. Similar to the increased incidence of HCC in the last decade from the epidemic of hepatitis C, ICC may occur from viral hepatitis and metabolic syndrome-related

Table 2 Recent phase Ⅱ studies of chemotherapy for biliary tract carcinoma

Agents	*n*	RR (%)	PFS (M)	MST (M)	Authors	Year
Gemcitabine						
1000mg/m^2, 30-min infusion	25	36		6.9	Gallardo	2001
	24	12.5	2.5	7.2	Lin	2003
	40	17.5	2.6	7.6	Okusaka	2006
Fluoropyrimidine						
Capecitabine	26	19		8.1	Patt	2004
S-1	19	21	3.7	8.3	Ueno	2004
S-1	40	32.5	3.7	9.4	Furuse	2008
Others						
Docetaxel	24	20	6.0	8.0	Papakostas	2001
CPT-11	36	8	2.7	6.1	Alberts	2002
Erlotinib	42	8	2.6	7.5	Philip	2006
Gemcitabine + fluoropyrimidine						
Gem/5FU	27	33	3.7	5.3	Knox	2004
Gem/5FU/LV	30	20	3.7	4.7	Hsu	2004
Gem/5FU/LV	42	12	4.6	9.7	Alberts	2005
Gem/capecitabine	45	31	7.0	14.0	Knox	2005
Gem/capecitabine	45	32	6.0	14.0	Cho	2005
Gemcitabine + platinum						
Gem/cisplatin	30	37	4.1	4.6	Doval	2004
Gem/cisplatin	40	28	4.7	8.4	Thongprasert	2005
Gem/cisplatin	29	35	3.0	11.0	Kim	2006
Gem/cisplatin	27	33	5.6	10.0	Park	2006
Gem/oxaliplatin	33	33	5.7	15.4	Andre	2004
Gem/oxaliplatin/bevacizumab	26	29	7.6		Clark	2007
Fluoropyrimidine + platinum						
Capecitabine/oxaliplatin	65	20	6.5	12.8	Nehls	2006
S-1/cisplatin	51	30	4.8	8.7	Kim	2007

RR: Response rate; PFS: Median progression-free survival; ST: Median overall survival; FU: Fluorouracil.

liver disease[72]. There are some reports that suggest the relationship between chronic hepatitis and peripheral mass-forming ICC[73]. These facts may indicate that ICC includes two different types pathologically and biologically: Peripheral mass-forming type (usually hepatitis-based) and central periductal-infiltrating type without hepatitis. However, further investigations are needed.

LONG-TERM SURVIVAL WITH REPEATED SURGERY AND CHEMOTHERAPY

Although the results of surgical resection for ICC patients with lymph node metastases are thought to be especially poor, the outcome of hepatectomy for these patients is comparable to that for patients without lymph node metastases in our series.

Forty-four patients with ICC, including 13 patients with lymph node metastases, underwent hepatectomy before 2006 in our institute. The survival rates of those patients after first hepatectomy are 51%, 29% and 22% for 3, 5 and 10 years, respectively. The survival rates of the patients with and without lymph node metastases are 42% and 51% for 3 years, and 28% and 29% for 5 years, respectively. There was no significant difference in the survival curves between groups. However, 11 out of 13 patients with lymph node metastases have recurrences after first hepatectomy (7 in residual liver; 2 in lung, lymph node, each; and 1 each in bone, brain, peritoneum). Five patients with lymph node metastases and 11 patients without lymph node metastases actually survived more than 3 years, and 4 of those 5 patients with lymph node metastases underwent repeated surgery for recurrences in the residual liver or the lung. Three of them also underwent adjuvant and/or neo-adjuvant chemotherapy. One patient who underwent four hepatectomies and 1 pulmonary resection combined with chemotherapy survived 6 years and 9 mo[74].

We also examined the results of 12 consecutive patients with unresectable advanced biliary tract carcinoma, including 8 patients with ICC in the other series of our patients. They were treated with first-line chemotherapy of S1/cisplatin combined with surgical resection and second-line chemotherapy of gemcitabine. MST of the patients was 15.9 mo. With S1/cisplatin therapy, 6 patients had a partial response based on the Response Evaluation Criteria in Solid Tumors guideline and 4 had a stable disease. Two patients with surgical resection after the therapy survived more than 4 years[75].

FUTURE PROSPECTS

Surgical resection is the only therapy for the cure of ICC patients. However, current resectability and prognosis after hepatectomy are not satisfactory. Further investigations should be conducted about the treatment for the recurrence after surgery and for patients with poor

prognostic factors, such as multiple tumors and lymph-node metastases.

Although the recurrence rate after hepatectomy is still high for the patients with ICC, the residual liver and the lung are the main sites of recurrence. Repeated surgery for the lesions could contribute to the survival of the patients with recurrences. Combined repeated surgeries and new effective regimens of chemotherapy could facilitate ICC patients for a long-term survival, even though without complete cure.

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