절제연 양성의 간내담관암에서 수술 후 항암화학방사선치료의 역할

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Postoperative Chemoradiotherapy for R1 Resected Intrahepatic Cholangiocarcinoma

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Background/Aims: To investigate the potential role of postoperative chemoradiotherapy (CCRT) after R1 resection of intrahepatic cholangiocarcinoma (IHCC).

Methods: Between January 2000 and December 2012, medical records of 18 patients who underwent curative surgery with R1 resection for IHCC were retrospectively reviewed.

Results: Median age was 68 years and 12 patients (66.7%) were male. Median tumor size was 5.0 cm (range, 2.2-11.0) and 12 patients (66.7%) had T3 or higher disease. Lymph nodes were involved in four patients (22.2%). Vascular invasion and perineural invasion were present in 10 (55.6%) and 12 patients (66.7%), respectively. Postoperative CCRT given with 5-fluorouracil or gemcitabine were delivered to 7 patients (38.9%). Median radiation dose was 50.4 Gy (range, 45-54). Univariate analysis showed that median loco-regional recurrence-free survival (LRRFS), progression-free survival (PFS) and overall survival (OS) were prolonged for patients treated with CCRT (median LRRFS; 5.6 months vs. not reached, $P<0.001$, median PFS; 5.6 vs. 8.3 months, $P=0.047$, median OS; 15.0 vs. 26.6 months, $P=0.064$).

Conclusions: Postoperative CCRT improved the loco-regional control and PFS in IHCC patients with R1 resection. Further study is warranted to validate the role of postoperative CCRT for these patients. (J Liver Cancer 2018;18:115-120)

Keywords: Intrahepatic cholangiocarcinoma; R1 resection; Chemoradiotherapy

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INTRODUCTION

Intrahepatic cholangiocarcinoma (IHCC) is the second most common cancer comprising 10-20% of all primary liver cancers.¹ While curative surgery gives the only chance of cure,² two thirds of the patients recurred after resection. Dominant pattern of failure is the loco-regional recurrence followed by simultaneous loco-regional and distant failures, and distant metastasis alone being the least common,³⁻⁶ which provides a justification for adjuvant radiotherapy. However, the role of adjuvant treatment for patients with resected IHCC has not been determined. There are limited clinical trial data to support a standard regimen for adjuvant treatment and there were controversial results about the benefit of adjuvant radiotherapy.^{2,7,8}

For a greater potential benefit from adjuvant treatment, identifying high-risk patients for recurrence is important. While a number of prognostic factors for recurrence including age, tumor size, multiplicity, vascular invasion, perineural invasion, lymph node status and resection margin status were suggested in IHCC,² several studies reported the association between the risk factors and potential benefit of adjuvant radiotherapy.^{4,5} Recently, Song et al.⁴ investigated to identify high-risk patients for the benefit of adjuvant radiotherapy after curative resection of IHCC. They reported that patients with advanced T stage or R1 resection had a poor loco-regional control.⁴ Here, we report the experience of post-operative chemoradiotherapy (CCRT) in IHCC patients with R1 resection.

METHODS

1. Patient selection

Between January 2000 and December 2012, medical records of 18 patients who underwent curative intent surgery with microscopic R1 resection for IHCC were retrospectively reviewed. Pathologic information including tumor size, grade, resection margins status, perineural invasion, vascular invasion and lymph node status were evaluated. TNM stage was classified using American Joint Committee on Cancer

(AJCC) staging system 7th Edition.⁹

2. Adjuvant treatment

According to the physician's preference, seven patients received adjuvant radiotherapy concurrently with chemotherapy. External-beam radiotherapy using mega-voltage equipment (6-15 MV X-ray) was given. Radiation field encompassed surgical margin plus 2 cm and regional lymph nodes (LN's). All patients underwent individualized computer-based treatment planning. Radiation dose ranged from 45 to 54 Gy (median, 50.4). Concomitant chemotherapy regimens were 2 cycles of 5-fluorouracil (500 mg/m²) for 3 consecutive days on 1st and 5th weeks of radiotherapy, twice daily capecitabine (650 mg/m²) or weekly gemcitabine (300 mg/m²). As for other 11 patients who did not receive radiotherapy, adjuvant chemotherapy was administered to two patients.

3. Follow up

The patients were followed-up with 3-4 months interval up to 2 years and 6 months interval thereafter. Overall survival (OS) was defined as the time from the date of surgery to either death or last follow-up. Local recurrence was defined as the recurrence of which the epi-center was within 2 cm from the resection margin. Regional LN was defined according to AJCC 7th Edition.⁹ Elsewhere hepatic recurrence was defined as the intrahepatic recurrence which excluded local recurrence. All of the recurrences were counted cumulatively. Loco-regional recurrence-free survival (LRRFS) was defined as the time elapsed from the date of surgery to the date on which local or regional failure occurs. Progression-free survival (PFS) was defined as the time from the date of surgery to any disease recurrence. Treatment toxicity was evaluated according to the common terminology criteria for adverse events (CTCAE) version 4.0. Statistical analysis was performed using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Patient and tumor characteristics

Median age was 68 years and 12 patients (66.7%) were male. Hemihepatectomy was performed in six patients (33.3%) and extent of resection was less than hemihepatectomy in eight (44.4%), more than hemihepatectomy or central hepatectomy in four (22.2%). LN dissection was performed in 11 (61.1%) patients. Median number of harvested LN was 2 (range, 1-12). Median tumor size was 5.0 cm (range, 2.2-11.0) and 12 patients had T3 or higher disease. LN's were involved in four patients. Vascular invasion and perineural invasion were present in 10 and 12 patients, respectively. Postoperative CCRT given with 5-fluorouracil, capecitabine, or gemcitabine were delivered to seven patients. Patient and tumor characteristics were listed in Table 1. For all variables, there were no significant differences between the two groups.

2. Follow-up

Median follow-up period was 16.8 months (range, 5.5-98.9). Sixteen patients were dead and two patients were alive. Both patients were treated with CCRT, and they had small tumors (2.2 and 3.4 cm, respectively) with no vascular invasion and LN-negative disease. No grade 3 or higher toxicities were observed in patients treated with CCRT.

3. Patterns of recurrence and survival

Sixteen patients had recurrence, and patterns of recurrence in the two groups were described in Fig. 1. Distant metastases occurred in 15 patients; non-regional LN metastases in 5, peritoneal seeding in 5, bone metastases in 3, and lung metastases in 3. Kaplan Meier analysis showed that median LR-RFS, PFS and OS were prolonged in patients treated with CCRT (LR-RFS; 5.6 months vs. not reached, $P<0.001$, PFS; 5.6 vs. 8.3 months, $P=0.047$, OS; 15.0 vs. 26.6 months, $P=0.064$) (Fig. 2).

DISCUSSION

This study showed an improved loco-regional control in patients treated with postoperative CCRT after R1 resection for IHCC. Despite the limited patient number, patients treated with CCRT had an improved PFS with statistical significance, implicating the possible role of CCRT in R1 re-

Table 1. On-going randomized trials

Variable	No CCRT (n=11)	CCRT (n=7)	P-value
Age			0.119
<60	4	0	
≥60	7	7	
Sex			1
Male	7	5	
Female	4	2	
Type of resection			0.232
Less than hemihepatectomy	6	2	
Hemihepatectomy	2	4	
Extended hemihepatectomy	3	1	
T stage			0.627
T1-T2	3	3	
T3-T4	8	4	
Size			0.63
<5 cm	4	4	
≥5 cm	7	3	
N stage			0.119
N0	3	4	
N1	4	0	
Nx	4	3	
Vascular invasion			0.63
No	4	4	
Yes	7	3	
Perineural invasion			1
No	4	2	
Yes	7	5	
Gross type			0.63
Mass forming	7	3	
Other	4	4	
Histologic differentiation			0.37
W/D	1	0	
M/D	8	6 [†]	
P/D	2*	0	

CCRT, concurrent chemoradiotherapy; W/D, well differentiated; M/D, moderately differentiated; P/D, poorly differentiated.

*One patient with adenosquamous histology was included; [†]One patient with unknown grade was excluded.

sected IHCC.

With the poor overall survival and high recurrence rate, adjuvant treatment has been considered after curative resection for IHCC. However, adequate subset of patients has not been determined who has a high risk of recurrence with the great potential benefit from adjuvant treatment. Various prognostic factors for survival or recurrence were proposed. These factors include tumor size, multiplicity, lymph node status, vascular invasion, perineural invasion and resection margin status.^{1-5,10,11} As complete resection is the only curative treatment, resection margin status is the important risk factor for survival or recurrence.^{4,11-17} Farges et al.¹³ reported that R1 resection was the strongest independent predictor of poor outcome in pN0 patients after curative surgery. Also, a margin width >5 mm was an independent predictor of survival among pN0 patients with R0 resection.¹³ Although ag-

gressive surgery to obtain R0 resection has been supported,¹⁸ the incidence of R1 resection was reported to be 8-24% after curative resection.^{1,3,4,11,13}

Given these observation, adjuvant radiotherapy for R1 resected patients could be advocated. Song et al.⁴ defined a local failure as the recurrence of which the epi-center was within 2 cm from resection margin, which is the potential target for adjuvant radiotherapy. In this study, R1 resected patients had high risks for loco-regional recurrence (relative risk, 3.34; $P=0.030$) and overall survival (relative risk, 5.113; $P=0.001$). Moreover, Gil et al.⁵ reported that after R0 resection, about 20% of the patients recurred within the potential target for radiotherapy.

In the current study, radiation field was defined as surgical margin + 2 cm within the liver plus regional lymph nodes. Our results showed an improved loco-regional control with CCRT, and there was no isolated in-field failure among the seven patients treated with CCRT. Without CCRT, however, all patients experienced loco-regional recurrences after R1 resection of IHCC.

In biliary tract cancers, several studies showed the advantage of adjuvant treatment.^{7,19,20} Horgan et al.⁷ reported a meta-analysis showing an improvement in OS with adjuvant treatment compared with surgery alone in bile duct cancers. In their study, chemotherapy or chemoradiation therapy was associated with a significantly greater benefit than radiation alone, with the greatest benefit observed in patients with

Figure 1. Patterns of recurrence according to the receipt of concurrent chemoradiotherapy (CCRT).

Figure 2. Loco-regional recurrence-free survival, progression-free survival and overall survival curves according to the receipt of concurrent chemoradiotherapy (CCRT).

lymph node-positive disease or R1 resection.⁷ However, only one study included patients with IHCC. Regarding IHCC, Shinohara et al.⁸ analyzed a total of 3,839 IHCC patients from Surveillance, Epidemiology, and End Results database. Although only one-fourth of patients had localized disease, patients treated with surgery and adjuvant radiotherapy had a prolonged survival than those treated with surgery alone (11.0 vs. 6.0 months).

Limited number of patients is the major limitation of this study. However, we tried to identify whether there were skewed risk factors between the two groups. Because patients with R1 resection have failed to catch the chance of cure, the absence of treatment guideline for these patients has been the great obstacle in real clinic. Despite the limited number of patients, this study is the first study to identify the effect of postoperative CCRT for R1 resected patients with IHCC, considering the low incidence and lower cases of R1 resection of IHCC. For further research, multi-institutional study is warranted.

In conclusion, our study showed an improved loco-regional control and PFS in patients treated with CCRT after R1 resection for IHCC. Further study is warranted to validate the role of postoperative CCRT for these patients.

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Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

- Hyder O, Marques H, Pulitano C, Marsh JW, Alexandrescu S, Bauer TW, et al. A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience. *JAMA Surg* 2014;149:432-438.
- Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. *JAMA Surg* 2014;149:565-574.
- Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg* 2008;248:84-96.
- Song S, Kim K, Chie EK, Kim S, Park HJ, Yi NJ, et al. Locoregional recurrence after curative intent resection for intrahepatic cholangiocarcinoma: implications for adjuvant radiotherapy. *Clin Transl Oncol* 2015;17:825-829.
- Gil E, Joh JW, Park HC, Yu JI, Jung SH, Kim JM. Predictors and patterns of recurrence after curative liver resection in intrahepatic cholangiocarcinoma, for application of postoperative radiotherapy: a retrospective study. *World J Surg Oncol* 2015;13:227.
- Hyder O, Hatzaras I, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, et al. Recurrence after operative management of intrahepatic cholangiocarcinoma. *Surgery* 2013;153:811-818.
- Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 2012;30:1934-1940.
- Shinohara ET, Mitra N, Guo M, Metz JM. Radiation therapy is associated with improved survival in the adjuvant and definitive treatment of intrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2008;72:1495-1501.
- Edge S, Byrd DR, Compton CC, Fritz AG, Greene F, Trotti A. *AJCC cancer staging manual*. 7th ed. New York: Springer-Verlag, 2010:201-205.
- Li T, Qin LX, Zhou J, Sun HC, Qiu SJ, Ye QH, et al. Staging, prognostic factors and adjuvant therapy of intrahepatic cholangiocarcinoma after curative resection. *Liver Int* 2014;34:953-960.
- de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol* 2011;29:3140-3145.
- Luo X, Yuan L, Wang Y, Ge R, Sun Y, Wei G. Survival outcomes and prognostic factors of surgical therapy for all potentially resectable intrahepatic cholangiocarcinoma: a large single-center cohort study. *J Gastrointest Surg* 2014;18:562-572.
- Farges O, Fuks D, Boleslawski E, Le Treut YP, Castaing D, Laurent A, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-IHCC-2009 study group. *Ann Surg* 2011;254:824-829.
- Yamashita Y, Taketomi A, Morita K, Fukuhara T, Ueda S, Sanefuji K, et al. The impact of surgical treatment and poor prognostic factors for patients with intrahepatic cholangiocarcinoma: retrospective analysis of 60 patients. *Anticancer Res* 2008;28:2353-2359.
- Nakagohri T, Kinoshita T, Konishi M, Takahashi S, Gotohda N. Surgical outcome and prognostic factors in intrahepatic cholangiocarcinoma. *World J Surg* 2008;32:2675-2680.
- Paik KY, Jung JC, Heo JS, Choi SH, Choi DW, Kim YI. What prog-

- nostic factors are important for resected intrahepatic cholangiocarcinoma? *J Gastroenterol Hepatol* 2008;23:766-770.
17. Murakami Y, Uemura K, Sudo T, Hashimoto Y, Nakashima A, Kondo N, et al. Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma. *Ann Surg Oncol* 2011;18:651-658.
 18. Ribero D, Pinna AD, Guglielmi A, Ponti A, Nuzzo G, Giulini SM, et al. Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. *Arch Surg* 2012;147:1107-1113.
 19. Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. *Surg Oncol Clin N Am* 2002;11:941-954.
 20. Kim MY, Kim JH, Kim Y, Byun SJ. Postoperative radiotherapy appeared to improve the disease free survival rate of patients with extrahepatic bile duct cancer at high risk of loco-regional recurrence. *Radiat Oncol J* 2016;34:297-304.