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Original Paper

Is Surgical Resection Justified for Advanced Intrahepatic Cholangiocarcinoma?

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Key Words

Intrahepatic cholangiocarcinoma · Intrahepatic metastasis · Lymph node metastasis · Surgical resection · Vascular invasion

Abstract

Backgrounds: Prognosis for patients with advanced intrahepatic cholangiocarcinoma (ICC) with intrahepatic metastasis (IM), vascular invasion (VI), or regional lymph node metastasis (LM) remains poor. The aim of this study was to clarify the indications for surgical resection for advanced ICC. ***Methods:*** We retrospectively divided 213 ICC patients treated at Kyoto University Hospital between 1993 and 2013 into a resection (n=164) group and a non-resection (n=49) group. Overall survival was assessed after stratification for the presence of IM, VI, or LM. ***Results:*** Overall median survival times (MSTs) for the resection and non-resection groups were 26.0 and 7.1 months, respectively (p<0.001). After stratification, MSTs in the resection and non-resection groups, respectively, were 18.7 vs. 7.0 months for patients with IM (p<0.001), 23.4 vs. 5.7 months for those with VI (p<0.001), and 12.8 vs. 5.5 months for those with LM (p<0.001). ***Conclusion:*** When macroscopic curative resection is possible, surgical resection can be justified for some advanced ICC patients with IM, VI, or LM.

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Introduction

Intrahepatic cholangiocarcinoma (ICC), i.e., cholangiocarcinoma located near the secondary or more distal branches of the biliary tree, is the second most common primary liver cancer after hepatocellular carcinoma [1, 2]. The incidence of ICC is increasing globally [3]. Surgical resection is the mainstay of curative treatment for selected ICC patients, and 5-year survival rates of 15%–40% have been reported [4–8]. Outcomes after the surgical resection of ICC are relatively well reported, and previous cohorts have identified intrahepatic metastasis (IM), vascular invasion (VI), and lymph node metastasis (LM) as significant negative prognostic factors [4–7]. Accordingly, the European Association for the Study of Liver (EASL) guidelines for ICC [8] discourage surgical resection for advanced ICC patients with a clinical diagnosis of IM, VI, or LM.

Few studies [7, 9] have compared the outcomes of patients undergoing surgical resection for ICC with those undergoing non-surgical treatments. Moreover, the survival benefits of surgical resection have not been compared among patients with IM, VI, or LM. At Kyoto University Hospital, advanced ICC patients with IM, VI, or LM are considered for surgery if macroscopically curative resection is possible. In the present study, we analyzed the outcomes of resection in ICC patients at our institution and reviewed the associated literature to assess the indication of surgical resection for advanced ICC patients with IM, VI, or LM.

Patients and Methods

Study Design

The present historical cohort comprised all 213 patients who were diagnosed with ICC in the Department of Surgery, Kyoto University Hospital, from January 1993 to December 2013. ICCs were defined as tumors that had developed from the intrahepatic bile duct at the secondary or more-distal branches. Advanced ICC was defined as those with IM, VI, or LM. Advanced ICCs were found in 145 patients (68%), and non-advanced ICCs were found in 68 (32%) patients. In total, 164 patients underwent surgical resection and 49 underwent non-surgical treatments. Consequently, patients were divided into resection (n=164) and non-resection (n=49) groups. Patients in whom macroscopically curative resection was deemed possible were indicated for surgical resection (depending on the patients' overall condition and/or liver function). Cases were considered to be inoperable when bulky para-aortic lymph nodes or uncontrollable distant metastases were observed. ICC was diagnosed in the non-resected patients using radiography. In resected patients, ICC was confirmed by histopathologic analysis. The study protocol was approved by the ethical committee of the Graduate School of Medicine, Kyoto University (E2334).

Study Variables

Radiological and clinicopathological data were collected from medical records at Kyoto University Hospital, and patients' age, gender, Child–Pugh classification, serum CA19-9 levels, IM, VI, LM, distant metastasis, and clinical stage were recorded. Cancer stages were categorized as I, II, III, or IV according to the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer classification [10]. In both groups, IM, VI, and LM status was determined using pretreatment computed tomography and/or magnetic resonance imaging examinations. ^{18}F-Fluorodeoxyglucose positron emission tomography-computed tomography was introduced in 2002 for preoperative evaluation [11]. Distant metastases were detected using radiology or exploratory laparotomy. Follow-up data were updated on January 1, 2015.

Statistical Analysis

Overall survival (OS) was defined as the period between the date of initial hospitalization and the day of death from any cause. Survival curves were estimated using the Kaplan–Meier method and were compared using the log-rank test. ICC patients were then stratified into groups with IM, VI, or regional LM, and univariate and multivariate hazard ratios [with 95% confidence intervals (CI)] were estimated using Cox models. Five potential confounders were inserted into the Cox models: surgical resection, IM, VI, LM, and distant metastasis [4–8]. Continuous variables were expressed as the median (range) and

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Table 1. Clinical characteristics of 213 ICC patients treated at Kyoto University Hospital between 1993 and 2013

Variable	Resection n=164	Non-resection n=49	p-value
Age (years)			0.26
Median	65	67	
Range	26–84	36–82	
Gender			0.91
Male	99 (60%)	30 (61%)	
Child–Pugh classification B/C	6 (4%)	12 (24%)	<0.001*
CA19-9 levels (U/ml)			0.0010*
Median	60.1	436.1	
Range	0–29682	0–40357	
IM	36 (22%)	19 (39%)	0.018*
Tumor distribution: bilobar	23 (64%)	14 (74%)	0.46
Tumor number ≥5	11 (31%)	8 (42%)	0.39
VI	66 (40%)	30 (61%)	0.0096*
Portal venous invasion	56 (34%)	30 (61%)	<0.001*
Hepatic venous invasion	28 (17%)	18 (37%)	0.0033*
Regional LM	46 (28%)	17 (35%)	0.38
Distant metastasis	15 (9%)	31 (63%)	<0.001*
AJCC/UICC classification			0.031*
Stage I	26 (16%)	0 (0%)	
Stage II	19 (12%)	7 (14%)	
Stage III	27 (16%)	10 (20%)	
Stage IV	92 (56%)	32 (65%)	

*Significantly different. AJCC/UICC=American Joint Committee on Cancer/Union for International Cancer Control.

were compared using the Mann–Whitney U test. Categorical variables were compared using χ^2 tests. All analyses were two sided, and differences were considered significant when p<0.05. Statistical analyses were performed using JMP ver. 11.2 software (SAS, Cary, NC, USA).

Results

Patient Characteristics

Baseline clinical features of the patients are listed in table 1. The patients in the non-resection group showed high serum CA19-9 levels, and patients with Child–Pugh B/C, IM, VI, and distant metastasis and stage II, III, or VI patients were more numerous in the non-resection group. Distant metastasis, intrahepatic spread, locally advanced disease, and the patients' overall condition precluded surgery in 31, 14, 13, and 3 cases, respectively (they overlapped). Treatments for the non-resected patients included systemic chemotherapy (n=36), intra-arterial therapy (n=9), radiotherapy (n=1), and best supportive care (n=3). In the resection group, 14 patients with resectable or controllable distant metastasis (stable disease with non-surgical treatment) underwent surgical resection, of which 12 had non-regional LM, 2 had controllable lung metastasis, and 2 had localized peritoneal metastasis (with some overlap). In addition, 51 patients in the resection group (31%) underwent adjuvant gemcitabine-based chemotherapy [12].

Survival after Surgical Resection for Advanced ICC

OS was significantly better in the resection group than in the non-resection group [median survival times (MSTs), 26.0 vs. 7.1 months; 3/5-year survival, 43%/35% vs. 3.7%/0%; p<0.001]. Eight patients who underwent surgical resection died during the postoperative course. In the IM, VI, and LM subgroups, MSTs for the resection and the non-resection groups were 18.7 vs. 7.0 (p<0.001), 23.4 vs. 5.7 (p<0.001), and 12.8 vs. 5.5 months (p<0.001), respectively (fig. 1a–c). Further, we analyzed OS according to the number of risk factors. In patients with one, two, and three risk factors, MSTs for the resection and the non-resection groups were 20.3 vs. 10.0 (p<0.001), 16.9 vs. 5.5 (p<0.001), and 14.1 vs. 7.6 months (p=0.032), respectively (fig. 2a–c). Multivariate analysis showed that the hazard ratio of surgical resection was 0.32 [95% CI, 0.19–0.53]. LM (hazard ratio: 1.87, 95% CI: 1.25–2.76) was another independent prognostic factor (table 2).These results indicate that surgical resection for ICC patients with IM, VI, or LM provided more survival benefit than non-surgical treatments.

Discussion

IM, VI, and LM were identified as important prognostic factors in recent studies [4–7, 13] and in a systematic review of surgical resection outcomes [14], and these findings were reflected in the EASL guidelines [8]. The EASL guidelines discourage surgical resection in clinically advanced ICC patients with IM, VI, or LM; however, our data suggest that surgical resection provides marked survival benefits over non-surgical treatments, even for advanced ICC patients with IM, VI, or LM. In our institution, MSTs of advanced ICC patients with clinical IM, VI, or LM were 18.7, 23.4, and 12.8 months after surgical resection and 7.0, 5.7, and 5.5 months after non-surgical treatments, respectively. Moreover, surgical resection independently benefitted survival, regardless of the presence of clinical IM, VI, or LM.

In the current study, the comparison of surgical resection and non-surgical treatments was influenced by patient selection bias. To assess the strength of our assertions, we conducted a literature review. The PubMed database was systematically searched for articles published in English between January 2000 and January 2015 using the term "ICC". As a result, 1178 studies were retrieved from database searches, and 9 were retrieved from reference lists. These studies were subjected to the following exclusion criteria: (1) less than 50 patients, (2) no assessment of prognostic factors, (3) mixed series of patients with other diseases, (4) performance of liver transplantation, and (5) performance of ablation therapy. Of the 1187 studies considered, 26 were deemed eligible according to our review criteria and are described in table 3. Reported MSTs were 25.5 months in resected ICC patients and 12.2 months in non-resected ICC patients. In stratified analyses, MSTs for resected and non-resected patients, respectively, were 12.5 and 5.2 months for patients with IM and 10.7 and 5.9 months for patients with LM. No studies reported MSTs of non-resected patients with VI; however, the MST for resected patients with VI was 15.5 months. Taken together, surgical resection in ICC patients with IM, VI, or LM provided a survival benefit over non-surgical treatments in all included studies. Therefore, careful selection and curative resection can improve the prognosis in advanced ICC patients with IM, VI, or LM.

Further analysis according to the number of risk factors showed that prognosis became poorer as the number of risk factors increased. However, surgical resection provided a survival benefit to ICC patients regardless of the number of risk factors present. Recently, a

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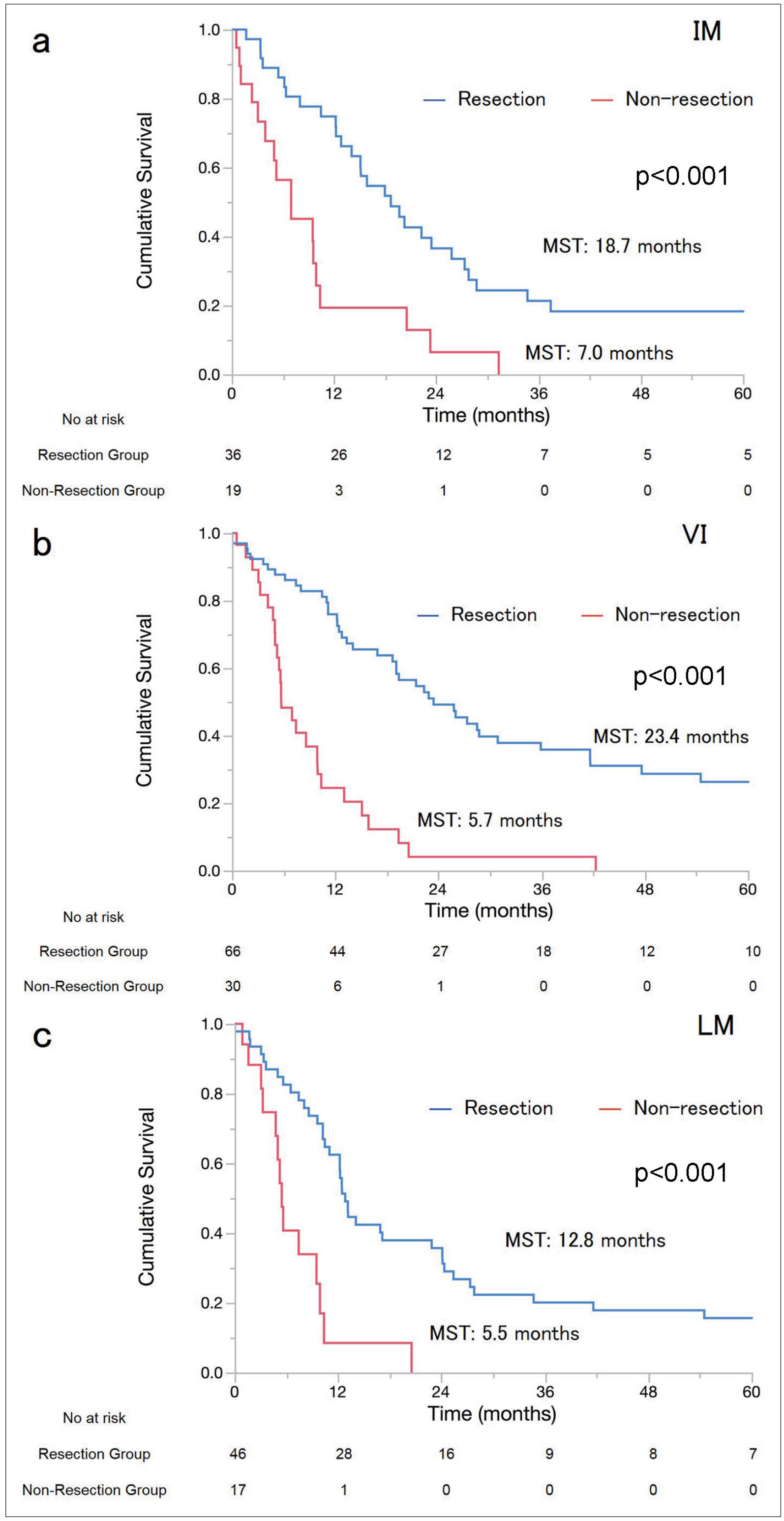

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Fig. 1. Survival curves of the resection and non-resection groups stratified by IM, VI, and LM (a–c). In patients with IM, VI, and LM, MSTs of resected and non-resected patients were 18.7 and 7.1 ($p<0.001$), 23.4 and 5.7 ($p<0.001$), and 12.8 and 5.5 months ($p<0.001$), respectively.

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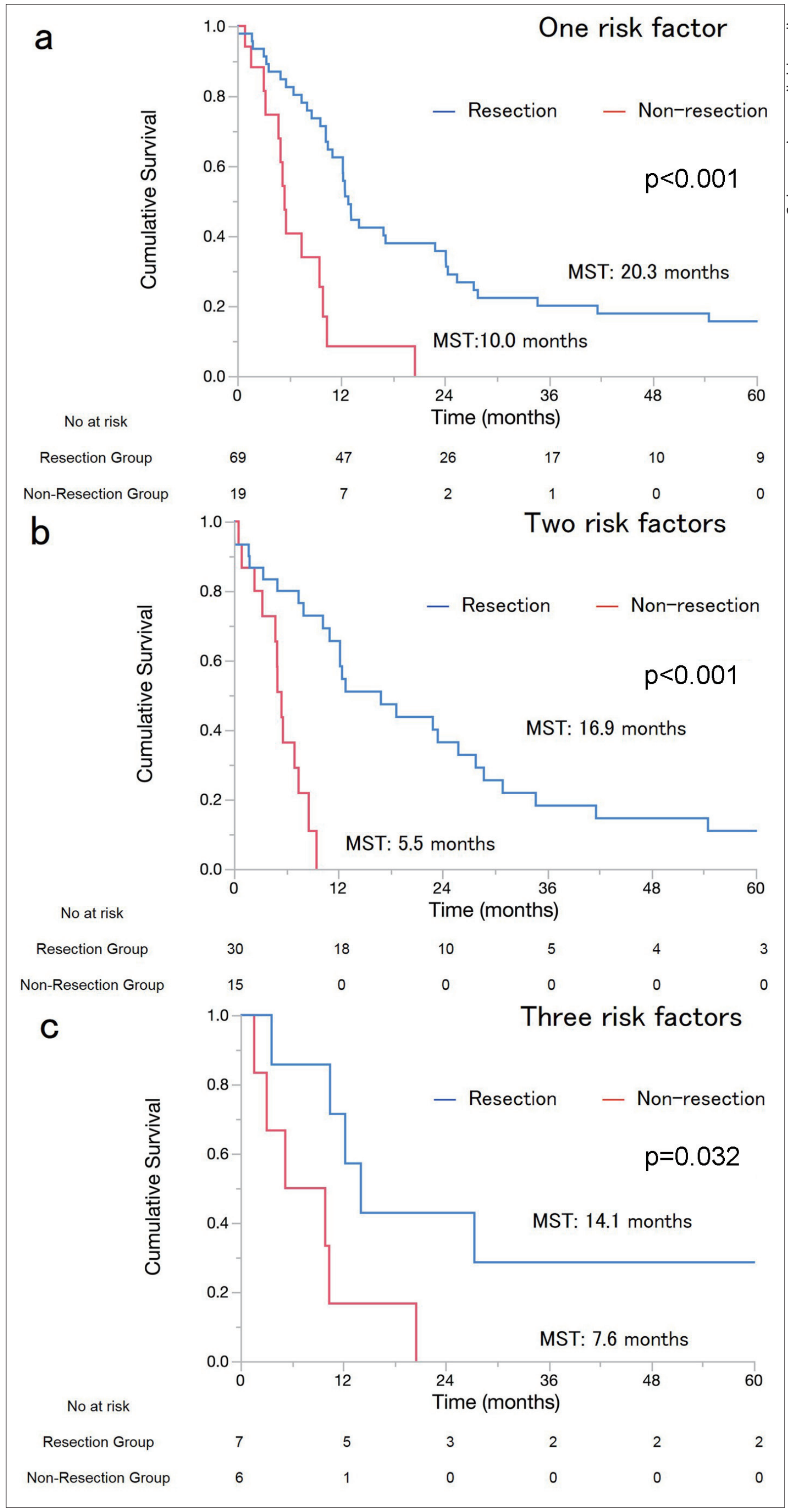

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Fig. 2. OS was additionally analyzed according to the number of risk factors present. In patients with one, two, and three risk factors (a–c), MSTs of the resection and non-resection groups were 20.3 vs. 10.0 (p<0.001), 16.9 vs. 5.5 (p<0.001), and 14.1 vs. 7.6 months (p=0.032), respectively. In patients who underwent surgical resection, there was no significant difference in survival among the patients with one, two, and three risk factors (p=0.46).

Table 2. Multivariate analysis

Variable	Hazard ratio	95% CI	p-value
Surgical resection	0.32	0.19–0.53	<0.001*
IM	1.50	1.00–2.10	0.051
VI	1.30	0.92–1.84	0.13
LM	1.87	1.25–2.76	0.0024*
Distant metastasis	1.19	0.70–2.00	0.52

*Significantly different.

new staging system was published by the Liver Cancer Study Group of Japan [15]. According to this new staging system, the presence of IM, VI, or LM strongly influences prognosis. The outcomes for patients with three risk factors were similar to those for stage IV B patients, which is the most advanced class in the new staging system. Surgical resection could provide patients with increased survival over non-surgical treatment even for patients with stage IV B disease. Our data also suggest that when macroscopic curative resection is possible, surgical resection can provide a survival benefit to some patients regardless of the progression of the disease or the disease stage.

In the present study, the sample size was small because of the rarity of ICC. Moreover, because the present study was not controlled by randomization, there was a selection bias between the resection and non-resection groups. Consequently, we conducted an exhaustive systematic literature review to assess the strength of our assertions. Although the 26 previously published studies reported results comparable to ours, they also might have been influenced by biases in patient selection. The present and previous data warrant further prospective studies to confirm the true survival benefits of surgical resection in advanced ICC patients with IM, VI, or LM. Another limitation of this kind of study is that both our data and previous data were from long-term studies. Treatment methods have consistently improved, particularly with regard to non-surgical treatment [16, 17], and this could affect the outcomes. Moreover, advances in imaging modalities could have affected patient selection as to whether surgical resection was possible. However, in the current analysis, surgical resection appears to provide survival benefits over non-surgical treatments even for advanced ICC patients with IM, VI, or LM.

In conclusion, surgical resection in ICC patients with IM, VI, or LM is associated with a longer life expectancy. It appears that surgical resection in advanced ICC patients can be justified, despite the recommendations of the EASL guidelines for ICC, and prospective trials to investigate the outcomes of surgical resection in such patients are warranted.

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Table 3. Clinicopathological characteristics, treatment, and clinical outcomes of patients assessed in the 26 index studies

Author (country)	Treatment	Number of patients	Mean age (years)	MST (months)	OS rate (%) 3y	OS rate (%) 5y	IM (%)/ MST (months)	VI (%)/ MST (months)	LM (%)/ MST (months)
Uenishi et al. [18] 2014 (Japan)	SR	233	-	23.8	39	31	28/ 12.5	72/ 17.2	37/ 14.3
Igami et al. [19] 2011 (Japan)	SR	61	61	24.6	-	34	31/ -	98/ -	38/ -
Nakagohri et al. [13] 2008 (Japan)	SR	56	66	22	42	32	18/ -	-/ -	38/ -
Luo et al. [20] 2014 (China)	SR	1333	54	14.4	25	17	36/ 10	15/ 14	28/ 9
Wang et al. [21] 2013 (China)	SR	367	53[a]	21	41	35	-/ -	15/ -	22/ -
Li et al. [22] 2011 (China)	SR	113	-	21	27	17	28/ -	22/ -	27/ -
Jiang et al. [7] 2011 (China)	SR	344	-	17.6	32	21	25/ 12.3	17/ 11.4	-/ -
Cho et al. [23] 2010 (Korea)	SR	63	61	25.5	51	32	32/ 14.5	-/ -	30/ 5
Choi et al. [24] 2009 (Korea)	SR	64	61	39	53	40	11/ -	58/ -	27/ -
Paik et al. [25] 2008 (Korea)	SR	97	57	53	53	31	10/ 9.5	-/ -	24/ 6.5
Bhudhisawasdi [26] 2012 (Thailand)	SR	171	56	7.6	19	13	37/ -	85/ -	-/ -
Ribero et al. [4] 2012 (Italy)	SR	434	65[a]	33	47	33	32/ -	53/ -	26/ -
Guglielmi et al. [27] 2009 (Italy)	SR	52	66	40	50	20	21/ 24	-/ 17	27/ 19
Lang et al. [28] 2009 (Germany)	SR	83	-	26	38	21	42/ -	41/ -	34/ -
Farges et al. [5] 2011 (France)	SR	212	63	28	43	28	59/ 21	44/ 22	37/ 15
Tamandl et al. [29] 2009 (Austria)	SR	69	-	25.5	35	-	29/ -	18/ -	19/ -
Hyder et al. [30] 2014 (US)	SR	514	59[a]	38.8	52	40	25/ -	24/ -	18/ -
Fisher et al. [31] 2012 (US)	SR	58	66[a]	23	-	-	21/ -	40/ 9.6	34/ 10.7
Endo et al. [32] 2008 (US)	SR	82	-	36	-	-	35/ 8	32/ 13	9/ 7
Spolverato et al. [33] 2014 (MN)	SR	557	60[a]	26.9	38	23	-/ -	39/ -	21/ -
de Jong et al. [6] 2011 (MN)	SR	449	61[a]	27.3	44	31	27/ 19	31/ 20.0	30/ 22.9
Park et al. [34] 2010 (Korea)	IAT	72	64	12.2	-	-	57/ -	-/ -	-/ -
Vogl et al. [35] 2012 (Germany)	IAT	115	60	13	10	-	70/ -	-/ -	-/ -
Hyder et al. [36] 2013 (US)	IAT	198	61[a]	13.2	22	16	53/ -	10/ -	11/ -
Chen et al. [37] 2010 (China)	RT	84	-	6.8	-	-	25/ 5.2	-/ -	85/ 5.9
Kim et al. [14] 2013 (Korea)	CT	67	58[a]	6.2	-	-	60/ -	-/ -	82/ -

[a] Age was described as median age. MST=median survival time; 3y=3 year; 5y=5 year; SR=surgical resection; MN=multinational; IAT=intra-arterial therapy; RT=radiotherapy; CT=chemotherapy.

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Disclosures

The authors declare that there are no conflicts of interest.

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