Ablative therapies for intrahepatic cholangiocarcinoma

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Abstract: Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy. Although surgical resection has been a cornerstone in the management of ICC, the efficacies of several non-surgical management strategies have been actively investigated and somewhat preferable outcomes have been reported for ablation therapies in selected cases. Nevertheless, because of the rarity of these tumors and the small number of studies, the clinical significance and actual role of ablation therapies in a multidisciplinary approach for ICC remain unclear. In this article, the reported outcomes of ablation therapies for ICC will be summarized and their potential indications will be discussed.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a relatively uncommon disease accounting for 5–30% of all primary liver malignancies (1). In the United States, however, the age-adjusted incidence of ICC has increased from 0.32 per 100,000 population in 1975 to 0.85 per 100,000 population in 2000 (2). Although surgical resection is the only curative treatment option, most patients with ICC are not candidate for surgery because most patients already have advanced disease at the time of presentation (3,4). As such, several non-surgical treatments for ICC have been investigated over the years to improve the survival outcomes of patients who are unfit for surgery. However, most previous studies regarding non-surgical treatments have failed to show satisfactory outcomes for ICC. Furthermore, tumor recurrence is common among patients with ICC, occurring in up to 70% even after curative resection (5), and the survival outcomes after recurrence are dismal. Because only a limited number of patients can proceed to repeat resection after recurrence, alternative non-surgical palliative management strategies need to be established.

Among several ablation therapies for solid tumors, radiofrequency ablation (RFA) has been increasingly used in the treatment of liver tumors, and its efficacy in hepatocellular carcinoma has been established (6-8). After an initial report of RFA for ICC (9), several case series have been reported, and a modest efficacy of RFA has been shown for unresectable ICC or recurrent ICC in selected cases (10,11). However, because of the rarity of this tumor, the clinical significance of ablation therapies for ICC remains unclear. In this article, the efficacy of ablation therapies for ICC will be reviewed and their role in multidisciplinary treatment will be discussed based on the reported evidence.

Indication and technical consideration

Given the oncological aggressiveness of ICC compared with hepatocellular carcinoma, surgical resection with an adequate lymphadenectomy remains the cornerstone of therapy for technically resectable disease. Therefore, in most previous studies, the efficacies of ablation therapies were mainly investigated among patients with unresectable ICC or recurrent ICC after surgery (12-21). The reported outcomes regarding ablation therapies for ICC are summarized in *Table 1*. In most previous reports, RFA was the mainstream treatment and microwave ablation was

Table 1 Reported clinical outcomes of radiofrequency ablation for intrahepatic cholangiocarcinoma

Authors	Country	Study period	Year	N	Size (cm)	Indication	Approach	Mortality (%)	Technical success rate (%)	Technical effectiveness (%)	Major complication (%)	Survival (%)		
												1-year	3-year	5-year
Chiou et al.	Taiwan	2002–2004	2005	10	1.9–6.8	Unresectable ICC	Percutaneous RFA	0	ND	80.0	0	ND	–	–
Carrafiello et al.	Italy	2004–2008	2010	6	1.0–5.8	Unresectable ICC	Percutaneous RFA	0	ND	66.0	0	ND	–	–
Kamphues et al.	Germany	2002–2008	2010	13	ND	Recurrent ICC	Stereotactic RFA	0	ND	ND	ND	92	52	–
Kim et al.	Korea	2000–2009	2011	13	0.8–8.0	Unresectable ICC	Percutaneous RFA	0	88.0	88.0	8.0	85	51	15
Giorgio et al.	Italy	2003–2010	2011	10	2.4–5.5	Unresectable ICC	Percutaneous RFA	0	ND	ND	0	100	83	83
Kim et al.	Korea	1999–2009	2011	20	0.7–4.4	Recurrent ICC	Percutaneous RFA	0	ND	95.0	10.0	70	21	–
Yu et al.	China	2006–2010	2011	15	1.3–9.9	Unresectable ICC	Percutaneous microwave	0	91.7	87.5	13.0	60	–	–
Xu et al.	China	1998–2010	2012	18	1.4–6.9	Unresectable ICC/recurrent ICC	Percutaneous RFA/microwave	0	92.0	92.0	5.0	36	30	30
Fu et al.	China	2000–2010	2012	17	2.1–6.8	Unresectable ICC/recurrent ICC	Percutaneous RFA	0	96.2	96.2	6.0	85	43	29
Haidu et al.	Austria	2004–2010	2012	11	2.0–10.0	Unresectable ICC/recurrent ICC	Stereotactic RFA	0	100.0	92.0	27.0	85	71	–
Zhang et al.	China	2007–2011	2013	77	ND	Recurrent ICC	Percutaneous RFA/microwave	0	100.0	94.7	3.9	70	21	–
Butros et al.	USA	1998–2011	2014	7	1.3–3.3	Unresectable ICC/recurrent ICC	Percutaneous RFA	0	100.0	89.0	0	100	60	20

ICC, intrahepatic cholangiocarcinoma; RFA, radiofrequency ablation; ND, no data.

only used in limited cases. RFA is usually performed under ultrasound guidance, and sufficient ablative margins of at least 0.5 to 1.0 cm surrounding tumors are required to secure the complete ablation of tumor nodules. To achieve an optimal ablative field, a single electrode is used for small lesions (usually measuring up to 2–3 cm in diameter) and multiple or clustered electrodes are used for large lesions (usually greater than 3–3.5 cm in diameter) (11). The reported technical success rate of RFA for ICC ranged from 80% to 100%. However, Giorgio *et al.* reported that it is difficult to achieve complete ablation during the 1st session when the tumor size exceeds 4 cm, while complete ablation was always achieved for smaller nodules equal to or less than 3.4 cm (16). In multivariate analyses in previous studies, tumor size was identified as the main factor predicting the initial effectiveness of RFA, as well as the survival outcomes after RFA (13,19).

Effectiveness of RFA

The technical effectiveness (i.e., complete ablation without local progression for at least 1 month), which was defined by the Society of Interventional Radiology reporting standards (22), has been reported to be 80% to 100% in previous studies. However, the local tumor progression rate after RFA was relatively high, ranging from 8% to 50% (12-15,17,19,20), and the pooled rate in a meta-analysis was reported to be 21% (95% CI, 13–30%) (11). The rate of major complication observed after RFA was 8% in the evaluable population, as shown in *Table 1*.

The pooled 1-, 3-, and 5-year survival rates in the meta-analysis were 82% (95% CI, 72–90%), 47% (95% CI, 28–65%), and 24% (95% CI, 11–40%), respectively (11). These data were compatible with the clinical outcomes recently estimated using the SEER database (23). Amini *et al.* reported that in reviewing 1,232 patients selected from the SEER database, only 64 (5.2%) patients underwent ablation therapy alone. Interestingly, they noted that the median survival of patients treated with ablation therapy was 20 months, which was worse than that of patients treated with resection but better than that of patients treated with radiation therapy alone (23). Although these outcomes are likely to be influenced by the differences in the baseline characteristics of the patients in each group, for a selected group of patients, RFA might confer a modest survival advantage, compared with other non-surgical treatment options including radiation therapy or chemotherapy.

Prognostic impact and role of RFA in multidisciplinary treatment

A multivariate analysis in the study using the SEER database (23) revealed that ablation therapy may have a preferable prognostic impact, compared with the best supportive care (BSC), with a hazard ratio (HR) of 0.57 (95% CI, 0.40–0.83), while surgery alone (HR, 0.46; 95% CI, 0.39–0.54) or surgery + radiotherapy (HR, 0.46; 95% CI, 0.35–0.60) were strongly correlated with a better survival outcome.

Given the separate indication in actual clinical settings between surgery and RFA, it is difficult to compare the efficacy of surgery and RFA directly for primary tumors. However, for patients with recurrent ICC after surgery, it has been reported that ablation therapy (RFA or microwave ablation) have been reported to have an overall efficacy similar to that of repeated hepatic resection especially in patients with tumors up to 3 cm in diameter (24). This observation is consistent with previous reports examining the use of ablation therapies for ICC, and suggests that although ablation therapy might be effective in selected patients with recurrent ICC, its indication should be limited according to tumor size (14,16).

Compared with surgery, a clear advantage of RFA is its lower invasiveness and lower morbidity rate. In the largest series comparing ablation therapies with repeated resection for recurrent ICC, the major complication rate was 3.9% after ablation therapies, while it was 46.9% after repeated resection (24). Therefore, in a selected population with small recurrent tumors, ablation therapies could be a first-line treatment comparable with surgical resection.

Although only limited evidence from a small number of studies has been reported because of the rarity of this tumor, ablation therapies (mainly RFA) could be a treatment of choice for selected cases of ICC (*Figure 1*). The indications for RFA should be determined based on the local expertise and availability of the equipment required for ablative therapies. Further studies involving a large cohort of patients are needed to refine the current indication criteria and our knowledge of ablative therapies for ICC.

Conclusions

Although surgical resection is the first choice of treatment for patients with resectable ICC, ablative therapies, mainly RFA, may have a modest prognostic impact for patients who are unfit for surgical resection at presentation or those
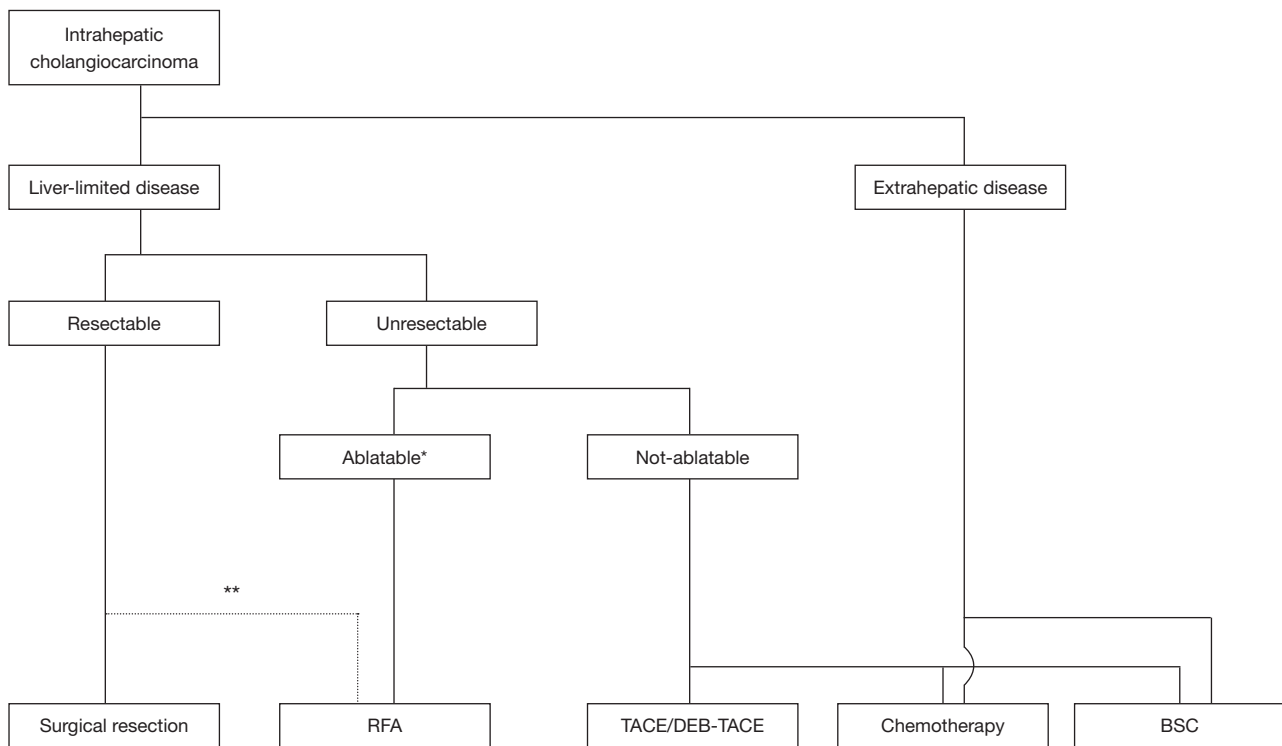
Figure 1 Algorithm for the selection of treatment for intrahepatic cholangiocarcinoma at Toranomon Hospital. *, possibility of complete ablation should be determined according to the local expertise and equipment; **, RFA can be used as a second choice for tumors up to 3 cm in diameter. RFA, radiofrequency ablation; TACE, transarterial chemoembolization; DEB-TACE, transarterial chemoembolization with drug-eluting beads; BSC, best supportive care.

with recurrence after surgery. Given the available data on the survival outcomes after RFA for ICC, ablation therapies could be a treatment of choice, especially for patients with small lesions up to 3 cm in diameter.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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