Hypofractionated Radiation Therapy: A Potential Option for Advanced Intrahepatic Cholangiocarcinoma

Junichi Shindoh, MD, PhD

Hepatobiliary Surgery Division, Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan

Intrahepatic cholangiocarcinoma (ICC) is an uncommon and aggressive primary hepatic malignancy. To date, surgery has been the only curative treatment option for ICC, and most cases of unresectable ICC have been managed with palliative chemotherapy, although the incidence of ICC has increased over the past decades.^{1,2} For patients with unresectable ICC confined to the liver, various locoregional treatments have been attempted in addition to systemic therapies, including hepatic arterial infusion therapy, transarterial chemoembolization with or without drug-eluting beads, or yttrium-labeled selective internal radiation therapy. Although encouraging results have been reported in several small case series, major limitations of such treatment include toxicity, availability, and lack of evidence supported by large prospective trials.

The “multidisciplinary treatment approach” has recently become a key word in the management of various aggressive malignancies. Because an aggressive treatment approach has been shown to be an important attitude for expecting longer survival outcomes in management of recurrent hepatocellular carcinoma (HCC)³ or colorectal liver metastases,⁴ it may also be important to have as many effective options as possible for better management of advanced and/or recurrent ICC.

With recent improvements in safe delivery of ablative doses of radiation for liver tumors, the role of radiation in management of liver cancers has been expanding rapidly, especially in the field of HCC.⁵ However, there is scarce evidence for ICC, partially because of the low incidence of

the disease. A recent multicenter phase II study of hypofractionated proton beam therapy for patients with localized, unresectable HCC and ICC demonstrated encouraging results with high local control rate for ICC,⁶ and based on these results, another multicenter study using hypofractionated external-beam radiation therapy (EBRT) for ICC has been carried out. Unfortunately, however, this study was closed early due to poor accrual of patients. Therefore, to look at the efficacy of hypofractionated proton or photon EBRT for patients with unresectable or locally recurrent ICC, Smart et al.⁷ recently conducted a single-center, retrospective study of 66 patients, including 32 patients who received proton beam radiation therapy from their previous study.⁶

In the present study,⁷ the authors report 2-year clinical outcomes of 66 patients with locally recurrent or unresectable ICC treated with hypofractionated proton or photon radiation therapy. Although use of proton radiation therapy showed a tendency towards improved 2-year survival rate compared with photon EBRT (65 vs 49%), the 2-year local control rate reached as high as 84% with relatively low severe toxicity rate (grade 3 < , 11%) in the entire cohort. Radiation-induced liver disease was observed in only one patient. These results are similar to those reported in another single-institutional study in 2016.⁸ Notwithstanding the sample size and single-institutional retrospective design, the current results suggest that both hypofractionated proton and photon EBRT could be delivered safely and may serve as a potential choice for treatment of unresectable ICC.

From the standpoint of the hepatobiliary surgeon, remaining concerns regarding such aggressive radiation therapy include the lack of effective treatment for local recurrence after radiation therapies and the technical difficulty of conversion surgery after extensive irradiation. In the present study,⁷ however, in-field recurrence was

relatively low (5 patients, 7.5%) and all the patients seemed to be managed adequately even in the cases with recurrence, achieving 2-year survival of 58%. Although the definition of “unresectable disease” varies considerably among surgeons and institutions, there are actually a small number of patients who present good response to radiation therapies and have potential to enjoy curative-intent treatment. Given the very high local control rate and encouraging results in terms of survival outcomes, hypofractionated radiation therapy could be an option for selected patients with marginally resectable or initially unresectable disease in the context of a multidisciplinary treatment approach. The present results reported by Smart et al. may warrant future multicenter, prospective studies for better management of advanced ICC.

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