



Proton beam therapy as a rising option in treating intrahepatic cholangiocarcinoma

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Intrahepatic cholangiocarcinoma (ICC) comprises about 10–15% of primary liver cancers, and the incidence is increasing (1,2). The only curative option is surgical resection, and the resectability rate at the time of diagnosis varies from 19% to 74% (3-6). Recent study showed the recurrence rate of 71% after curative resection of ICC, and 59.8% of them had local recurrence only (7). Unresectable ICC has a poor survival which the median overall survival (OS) is around 3 months when untreated (8) and palliative chemotherapy has shown survival benefit. ABC-02 trial showed biliary tract cancer treated with gemcitabine plus cisplatin had better survival than those treated with gemcitabine only (9), and now considered as the first choice chemotherapy in the treatment of unresectable or recurrent ICC.

Hepatic artery based therapy such as hepatic arterial infusion (HAI), transarterial chemoembolization (TACE), drug-eluting bead TACE (DEB-TACE) and transarterial radioembolization (TARE) is performed to deliver high dose of systemic agents (or radiologic agents) to the target lesion while minimizing systemic adverse events. A meta-analysis showed cumulative median OS of 22.8 months with HAI, 12.4 months with TACE, 12.3 months with DEB-TACE and 13.9 months with TARE (10). Recent study by Konstantinidis *et al.* showed improved median OS upto 30.8 months in unresectable ICC patients treated with HAI plus systemic chemotherapy (11). These results on HAI are strikingly good compared to the median OS of 11.7 months in ABC-02 trial. However, most of the studies of HAI have

retrospective nature and do not include the information of vascularity of the tumor. Another weakness of HAI is the invasive nature which includes surgical implantation of the infusion pump.

As for non-invasive modality, radiation therapy has been used in unresectable ICC cases. External beam radiotherapy (EBRT) was reported to have tumor response around 30%, offering a survival advantage. However, complications such as gastrointestinal symptoms and radiation induced hepatitis were also reported. Stereotactic body radio therapy (SBRT) has more precise targeting, enabling larger doses of radiation. Survival after SBRT was comparable to EBRT, yet having more significant adverse events such as gastrointestinal bleeding, hepatic failure (12,13). Proton-beam therapy (PBT) has been used to reduce radiation exposure to adjacent organs achieving concentrated dose to the target tumor, and a study of PBT including small group of ICC patients reported similar outcomes compared to SBRT, yet not giving a clear conclusion due to the small size of subjects (14).

In the current study published in *Journal of Clinical Oncology*, Hong *et al.* evaluated the efficacy and safety of PBT in patients with hepatocellular carcinoma (HCC) and ICC (15). A total of 43 patients with biopsy proven unresectable or locally recurrent ICC patients were included in this study and 39 were analyzed. Median tumor volume was 133.7 mL and median dose of 58.0 GyE in 15 fractions was delivered. Two-year local control rate was 94.1% in ICC patients, resulting in median progression free survival (PFS) of 8.4 months and median OS of 22.5 months.

The 1-year and 2-year OS rates were 69.7% and 46.5%, respectively. Three patients (7.7%) experienced grade 3 radiation-related toxicity, which was liver failure, gastric ulcer, and elevated bilirubin. There were no grade-4 or grade-5 radiation-related toxicities.

Survival results are encouraging, as median OS of 22.5 months is remotely better than that of the current standard treatment gemcitabine plus cisplatin (9), and rather close to the median OS of 27 months in patients with resected ICCs (16). As comparison with radiation therapy, studies of SBRT reported median OS shorter than 12 months (12,13) which is nearly half of that of PBT. However survival comparison should be interpreted with caution since the current study excluded subjects with extrahepatic disease while ABC-02 trial and two SBRT studies included such subjects with a lack of subgroup survival analysis. Only HAI has a comparable survival to the current study in unresectable ICC patients, with a cumulative median OS with 22.8 months in a meta-analysis (10) and 30.8 months for HAI plus systemic chemotherapy in liver confined ICC patients in a recent study (11).

However, survival results with PBT on cholangiocarcinoma are inconsistent in multiple studies. Makita *et al.* reported PBT for mixed etiology of cholangiocarcinoma (including six ICCs) had median OS of 12 months with a median dose of 68.2 GyE (14). Another study conducted by Ohkawa *et al.* included 20 unresectable ICC patients and reported to have median OS of 27.5 months in curative intent group (n=12), and 9.6 months in incurative intent group (n=8) using a median dose of 72.6 GyE (17). Patient selection criteria differs in these three studies including the current one, and this could be an explanation to the substantial differences in survival time and further investigation is warranted to establish the indications of PBT.

PBT looks quite tolerable in the current study with a 7.7% rate of grade 3 radiation-related toxicity. Since SBRT has been reported to have 7% grade 3 toxicity with a reference value of 17% (13), PBT protocol in current study seems to be at least as safe as SBRT. Previous study using PBT for ICCs reported 13% events (grade 3 or higher) per patient with a median dose of 72.6 GyE, and the other study reported 29% events per patients with a median dose of 68.2 GyE. A percentage of 29% events per patients is quite high and is in range of that of HAI with 35% events per patients with a 95% confidential interval of 0.22 to 0.48 (10). Grade 3 or higher events per patient is 0.077 in current study, which is significantly lower than the previous studies. This could be a result of dose-related nature of radiation

toxicity and regarding three studies, the upper margin of the optimal dose of PBT is likely to be under 70 GyE.

Recent studies elucidates the effectiveness of PBT in the treatment of ICCs and this well designed trial conducted by Hong *et al.* shows a surprising survival benefit in selected patients with ICC. Yet the recent version [2, 2016] of NCCN practice categorizes as locoregional therapy with a category 2B recommendation. ESMO guideline also states radiotherapy as a “may be considered” treatment for localized disease (18). We expect further accumulation of evidence regarding PBT for ICCs and looking forward to the following phase III trial.

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