Editorial

Management of Hepatocellular Carcinoma in Japan: Current Trends

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Editor Liver Cancer

The results of the 20th Nationwide Follow-up Survey of Primary Liver Cancer in Japan were recently published by the Liver Cancer Study Group of Japan [1]. The report included data on 21,075 patients newly registered at 544 institutions across Japan over a 2-year period from January 1, 2008, to December 31, 2009, in addition to 40,769 previously followed patients. Since its establishment in 1965, the Liver Cancer Study Group of Japan has been conducting biennial nationwide liver cancer surveys, with the results of each of the previous 19 surveys published in international journals. The most recent survey, which includes hepatocellular carcinoma (HCC) patients who registered in 2008 and 2009, is no exception, and the basic statistics and results of analysis of follow-up data were reported in *Hepatology Research* in 2019 [1].

A summary of the findings is as follows. Cases of early-stage HCC have become the majority, with an extremely small number of cases comprising advanced or end-stage liver cancer due to the established nationwide surveillance program in the early 1980s. The initial treatment modality was resection in 37.7% and ablation in 28.4% of patients, meaning that curative treatment was performed in as many as 66.1% of patients. Transarterial chemoembolization was performed as the initial treatment modality in 27.5% of patients [1]. The proportion of patients who underwent curative treatment is higher than the previously

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Fig. 1. Initial treatment modality for HCC detected between 2008 and 2009 ($n = 18,458$). HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; BSC, best supportive care. Modified from Kudo et al. [1].

Fig. 2. Overall survival according to grade of portal vein invasion in patients with hepatocellular carcinoma treated with surgical resection ($n = 29,081$). Median OS in patients with Vp0, Vp1, Vp2, and Vp3/Vp4 are 97, 61, 26, and 16 months, respectively; 5- and 10-year survival rates in patients with Vp0, Vp1, Vp2, and Vp3/Vp4 are 67, 51, 33, and 25, and 43, 29, 22, and 20%, respectively. mOS, median overall survival; M, months. Modified from Kudo et al. [1].

reported figure [2]. Japan was an early adopter of hepatic arterial infusion chemotherapy (HAIC), and this treatment was performed in 4.5% of patients with advanced HCC in the 20th survey (Fig. 1) [3, 4]. Because the molecular targeted agent, sorafenib, was approved in Japan in 2009, the proportion of patients who underwent systemic therapy was still low (0.9%). In addition, the proportion of patients who received only best supportive care as the initial treatment was 0.9%, indicating that some form of therapy was offered to many patients in

Fig. 3. Overall survival according to serum AFP level in patients with hepatocellular carcinoma treated with surgical resection ($n = 28,717$). mOS, median overall survival. Modified from Kudo et al. [1].

Japan after their initial diagnosis [5]. This was also true for Child-Pugh grade C and Barcelona Clinic Liver Cancer (BCLC) stage D; the proportion of patients who received best supportive care as the initial treatment after initial detection of HCC was extremely low (0.9%) [5, 6].

Portal vein tumor thrombosis was revealed to be a factor strongly associated with poor prognosis. When the overall survival (OS) rates of HCC patients who had undergone resection were compared by severity of portal vein invasion, median OS was found to decrease according to the extent of invasion: 97 months in patients with no portal vein invasion (Vp0), 61 months in those with Vp1, 26 months in those with Vp2, and 16 months in those with Vp3–Vp4 (Fig. 2). In addition, AFP level is also a strong predictor of prognosis and can serve as a prognosticator. When the OS of 28,017 HCC patients who had undergone hepatectomy was compared by serum AFP level, median OS decreased as AFP level increased: 114 months in patients with an AFP level ≤ 20 ng/mL, and 27 months in those with an AFP level $> 10,000$ ng/mL (Fig. 3). These results clearly show that portal vein invasion and AFP level are extremely important predictors of prognosis as well as prognostic factors in patients with HCC.

Comparison of median OS across four 8-year periods (registration period I, 1978–1985; period II, 1986–1993; period III, 1994–2001; and period IV, 2002–2009) shows clear improvement in median OS over the years: 5 months in period I, 25.6 months in period II, 43.0 months in period III, and 60.8 months in period IV (Fig. 4). Five-year survival rate also steadily improved: 11.9% in period I, 25.5% in period II, 39.7% in period III, and 50.4% in period IV. These data show a marked improvement in HCC prognosis compared with the results of the previous survey [2]. The above survival results were of patients in Japan with HCC at any stage (from BCLC stage 0 to stage D). It is clear that the complete establishment of a nationwide surveillance program increased the number of patients whose HCC was detected at an early stage; consequently, more HCC patients were able to receive curative therapy. This means that more patients benefited from curative treatment, which resulted in prolonged survival.

Fig. 4. Improvement of overall survival in all registered patients ($n = 157,758$) between 1978 and 2009 (all patients: BCLC stage 0, A, B, C, and D). Modified from Kudo et al. [1].

Japan leads the world in the outcome of liver cancer treatment, having a considerably higher 5-year survival rate compared with South Korea (18.9%) [7], Taiwan (20–22%), and the USA (10–15%) [8–11]. With the approval of sorafenib in 2009 followed by other targeted agents such as lenvatinib, regorafenib, or ramucirumab, a further increase in survival is expected in Japan. The surveillance system and curative treatment approach for HCC in Japan is recognized as a world-leading model [12–14], but HAIC may also have contributed to improvements in prognosis, especially in patients with macrovascular invasion [3]. However, the role of HAIC might be changed in an era of combination immunotherapy, such as atezolizumab plus bevacizumab [15].

Statement of Ethics

Ethical approval was not applicable.

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