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Editorial

Very-early-stage Hepatocellular Carcinoma, Are We at Long Last on Route for Achieving Better Patient Outcomes?

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Hepatocellular carcinoma (HCC) represents ~90% of the primary liver cancer cases, and 90% of HCC cases occur in patients with chronic liver disease.[1] It also represents the sixth most common cancer (4.7%) and the third leading cause of cancer-related death globally (8.3%).[2] More troubling, the global incidence and mortality rates have been increasing since 1990.[3] In the United States, the highest average annual percentage change (known as AAPC) reported between 2000 and 2012 involved individuals between 55 and 59 years of age (AAPC: 8.9%; 95% confidence interval: 7.1–10.7%).[4]

The current European Association for the Study of the Liver (commonly known as EASL) guidelines advise treatment assignment according to tumor stages following the Barcelona Clinic Liver Cancer (BCLC) staging system.[5] The concept of very-early or stage 0 classification was not introduced until the 2003 BCLC modification.[6] Surgical resection or image-guided ablation are the first-line therapies recommended in these set of patients.[5] The reported overall survival (OS) at 5 years after surgical resection is 71.1%, with a 5-year recurrence rate of 43.3%.[7] In patients excluded from surgery with Child class A, the reported 5-year survival rate is 61% and 5-year recurrence rate is 81%.[8]

Since patients with HCC BCLC stage 0 and A are deemed curable, such high recurrence rates are rather dismal and attempts are being made to improve patient outcomes. An interventional review explored chemotherapy, chemoembolization, internal radiation, and retinoids as neoadjuvant or adjuvant therapy after surgical resection and did not find enough evidence of their efficacy,[9] and hence are not currently advised.

Sorafenib, a multikinase inhibitor that targets receptor tyrosine and serine/threonine kinases to inhibit tumor growth and angiogenesis,[10] was shown in a phase II trial to have efficacy in patients with non-operable HCC.[11] A phase III double-blind placebo-controlled trial was then conducted and showed that sorafenib conferred a median OS of 10.7 months (hazard ratio: 0.69; 95% confidence interval: 0.55–0.87; $p<0.001$).[12] It was in the second BCLC modification, published in 2008, that sorafenib was incorporated as a first-line treatment option for BCLC stage C patients.[13]

A very large multicenter, phase III, double-blind, placebo-controlled trial was conducted to assess the efficacy and safety of sorafenib as an adjuvant therapy for both surgical resection and local ablation; results were disheartening, as no efficacy was found.[14] However, other smaller trials have shown more promising results.

A meta-analysis[15] was conducted to answer this question. Overall, the combined therapy showed significantly higher 1-, 2- and 3-year survival rates and an odds ratio of 2-year recurrence of 0.40 (95% confidence interval: 0.18–0.87). It is to be noted that the rate of adverse events was also higher for the combination therapy group, especially for that of hand-foot syndrome.

The results of this meta-analysis should be analyzed with caution. First, only three out of the fifteen studies were randomized controlled trials (commonly referred to as RCTs). Furthermore, the largest RCT[14] conferred great heterogeneity to the results. This was also the only trial which included some non-Asian patients, and HCC etiology may vary in different geographical regions, making results not applicable to all populations.

Some new light has been shed over the question of how to improve OS and decrease recurrence rates in candidates for potentially curative treatments. Nevertheless, the question remains largely unanswered, and a recommendation to include adjuvant treatment with sorafenib in the treatment of stage 0 or Child A patients cannot yet be made. High-quality RCTs, including diverse populations and with long-term follow-up are needed.

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