An Update on Randomized Clinical Trials in Hepatocellular Carcinoma

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KEYWORDS

• Hepatocellular carcinoma • Randomized trials • Review • Evidence-based medicine • Management

KEY POINTS

- Choice of treatment modality relies on consideration of tumor stage, liver function, performance status, and comorbidities.
- There has been no definitive comparison of transplantation, surgical resection, and local ablation.
- Radiofrequency ablation is currently the preferred technique for local ablation.
- Transarterial chemoembolization is currently the preferred technique for regional therapy, and confers survival benefit compared with best supportive care.
- For advanced disease, the standard of care in the first-line setting is sorafenib. Regorafenib has recently shown survival benefit in the second-line setting.

INTRODUCTION

The management of hepatocellular carcinoma (HCC) remains challenging on several accounts. First, most patients harbor background liver cirrhosis, which complicates treatment choice due to risk of liver failure. Second, HCC is driven by a variety of causes, including viral hepatitis, alcohol, and fatty liver disease, which may explain variation in the underlying biological mechanisms and treatment responses in different populations. Third, there are numerous treatment options to choose from. The Barcelona Clinic Liver Cancer classification provides a framework for treatment selection.[1] Early-stage disease is usually amenable to curative approaches, such as liver

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transplantation, surgical resection, and local ablation. Noncurative approaches include regional, radiation, and systemic therapy. Ultimately, treatment choice requires careful consideration of tumor extent, performance status, and underlying liver function, and is commonly determined by multidisciplinary team consensus.

This article reviews the evidence from randomized clinical trials that lay the foundation for contemporary HCC management. A discussion of prevention and screening trials, followed by the supporting data for the aforementioned treatment modalities are presented. Much of the literature remains controversial because many randomized trials are small and underpowered, with varying selection criteria, and are often single-institution studies based on specific populations. The emphasis is on those randomized clinical trials that have defined the current treatment algorithm.

PREVENTION AND SCREENING

Screening for HCC has become standard practice for high-risk patients, such as those with established cirrhosis or viral hepatitis. The key evidence supporting this comes from a large randomized trial conducted in China in the early 1990s.[2] A total of 18,816 subjects with known hepatitis B infection were randomly assigned to either screening with 6-monthly alpha-fetoprotein testing and ultrasonography, or no screening. Despite low compliance with screening, there was a significant reduction in mortality from HCC in the screened group (83.2 per 100,000) compared with controls (131.5 per 100,000), corresponding to a statistically significant mortality ratio of 0.63. This mortality reduction was attributed to the detection of HCC at an earlier stage in the screened group, in which tumors were still amenable to a curative approach.

Beyond screening of infected hepatitis B patients, it has been demonstrated that antiviral suppression significantly reduces the incidence of HCC. In the seminal trial evaluating the efficacy of lamivudine for chronic hepatitis B, 651 subjects were randomly assigned to either lamivudine or placebo for a maximum of 5 years.[3] HCC occurred in 4% of the lamivudine group versus 7% of the placebo group (hazard ratio [HR] 0.49, $P = .047$). There was a similar reduction in hepatic decompensation events. Previous prevention studies in hepatitis B were inconclusive but were based on less effective interferon therapy. Based on these data, antiviral therapy is used to delay progression of liver disease and reduce complications such as HCC.

For patients with hepatitis C, treatment has historically consisted of pegylated interferon and ribavirin. Multiple studies have assessed treatment effect on HCC risk. Meta-analysis of pooled data from 20 studies, including 4 randomized controlled trials, revealed a favorable and statistically significant risk ratio of 0.43 in treated hepatitis C subjects.[4] Notably, this benefit was driven by the subjects who achieved sustained virologic response and there was no benefit of ongoing therapy for nonresponders. The new generation of potent direct-acting antivirals, such as ledipasvir or sofosbuvir, is expected to yield further benefits, although data are still emerging.

TREATMENT

Transplantation

With rare exceptions, HCC is the only solid organ malignancy in which curative transplantation is a treatment option. This is made possible by the propensity of early HCC to spread locally instead of distantly, and the technical capabilities of liver transplantation surgery. Transplantation affords the unique benefit of simultaneously addressing both the tumor and the underlying tumorigenic liver. Eligibility for orthotopic liver transplantation is traditionally based on Milan criteria (solitary lesion 5 cm or less, or