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Radiotherapy for Hepatocellular Carcinoma

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For patients with unresectable or medically inoperable hepatocellular carcinoma, there are many local and regional therapies available, including stereotactic body radiotherapy, radiofrequency ablation, and transcatheter embolic approaches. This article will describe these treatment options and review the current comparative literature, suggesting that stereotactic body radiotherapy provides similar or better tumor control and a favorable side effect profile.

Semin Radiat Oncol 28:277–287

Introduction

Primary cancers of the liver account for 745,000 deaths annually, representing the second leading cause of cancer death worldwide.[1] In the United States, 80% of primary liver cancers are hepatocellular carcinoma (HCC) and the incidence is increasing. The burden of disease varies according to demographics and risk factors, including hepatitis B and C, alcoholic cirrhosis, and non-alcoholic fatty liver disease.[2]

There is limited consensus regarding optimal therapy for nonmetastatic HCC that is not amenable to curative resection or transplantation. A variety of liver-directed therapies have emerged for this population, including locally ablative therapies, such as radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT); as well as regional approaches, such as bland transcatheter arterial embolization (TAE), transcatheter arterial chemoembolization (TACE), and transcatheter radioembolization (TARE). The optimal selection and timing of liver-directed therapy can be complex. Considerations can include the availability of treatments, tumor burden, arterial accessibility, proximity to vasculature or hollow viscera, and baseline liver function (Fig. 1). Several treatment algorithms have been developed, and the Barcelona Clinic Liver Cancer (BCLC) system is one of the most popular (Fig. 2, top). Radiotherapy (RT) is notably absent from this algorithm,[3,4] although this article will discuss the potential addition of RT as an option in several clinical scenarios (Fig. 2, bottom).

Although HCC is a radiosensitive tumor, utilization of radiation has historically been limited by the relative sensitivity of normal liver parenchyma.[5-7] SBRT represents a significant advance in liver radiation, improving the therapeutic ratio by limiting the dose to functioning liver parenchyma, and escalating dose to the tumor. A growing body of literature supports the use of SBRT as an effective locally ablative therapy for HCC with a favorable toxicity profile.[8-11] Using highly conformal techniques (intensity modulated radiotherapy with photons or proton therapy), fractionated radiotherapy may experience a resurgence, taking advantage of more favorable radiobiology to escalate doses to tumors while maintaining acceptable normal tissue doses.[12]

This review summarizes the available clinical data regarding radiotherapy for HCC, with a focus on local control (LC), treatment tolerability, and efficacy compared with other commonly used modalities. In addition, we will discuss how SBRT may fit into this overall management algorithm. Clinical scenarios where SBRT may offer a comparative advantage, including large tumor diameter, presence of portal vein tumor thrombus (PVTT), and tumors near vasculature, are also discussed.

Underlying Liver Disease

Comorbid cirrhosis is present in approximately 80% of patients with HCC and is the principle risk factor for development of HCC.[13] One-year survival probabilities for patients with Child-Pugh (CP) A, B, and C cirrhosis, in the absence of HCC, are approximately 95%, 80%, and 45%, respectively.[14] Liver dysfunction is also associated with profound morbidity and diminished quality of life (QoL).[15,16] Furthermore, second distinct tumors are common after successful treatment of localized HCC due to the field cancerization effects of cirrhosis and viral hepatitis.[17-19] Thus, progressive cirrhosis and second primary HCCs represent major competing causes of morbidity and mortality.[14,20] This problem is compounded in patients who have been heavily pretreated with liver-directed therapy. Therefore, preservation of normal liver parenchyma is a priority for

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Conflict of interest: None.

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https://doi.org/10.1016/j.semradonc.2018.06.005

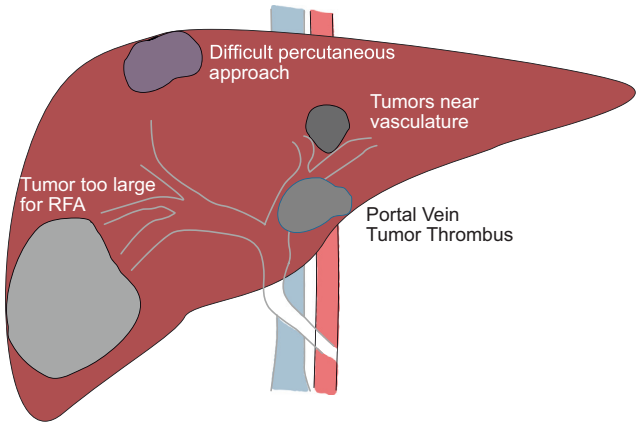

Figure 1. Situations in which SBRT may be favored over RFA or TACE.

liver-directed therapy, and assessment of liver function is critical for appropriate patient selection, estimation of prognosis, and safe treatment. Among patients with severely impaired liver function, the risks of therapy with any modality, including radiotherapy, may exceed the potential benefits.[21,22] Thus, understanding these competing risks and collaborating closely with hepatology is imperative.

Natural History

The natural history of untreated advanced HCC is best described by the pooled results from the control arms of 2 randomized clinical trials. Among 102 patients, 65 were CP A, 34 were CP B, and 3 were CP C. Three-year overall survival (OS) was 28%; performance status, constitutional syndrome, vascular invasion, and extrahepatic spread were predictors of OS on multivariate analysis. Patients with at least 1 risk factor had 3-year OS of 8% compared with 50% among those without any risk factors. At 3 years, 80% of patients developed a complication related to liver failure and 76% experienced deterioration in CP classification.[23] It is important to keep this in mind when deciding whether tumor-directed therapy is indicated, although unfortunately we still do not quite understand the competing effects of cirrhosis progression vs tumor progression.

Patient Stratification

A variety of staging and risk stratification systems have been developed for HCC. Clinical staging systems such as the Okuda, Cancer of the Liver Italian Program score, and BCLC systems are the most relevant for radiation oncologists, as patients under

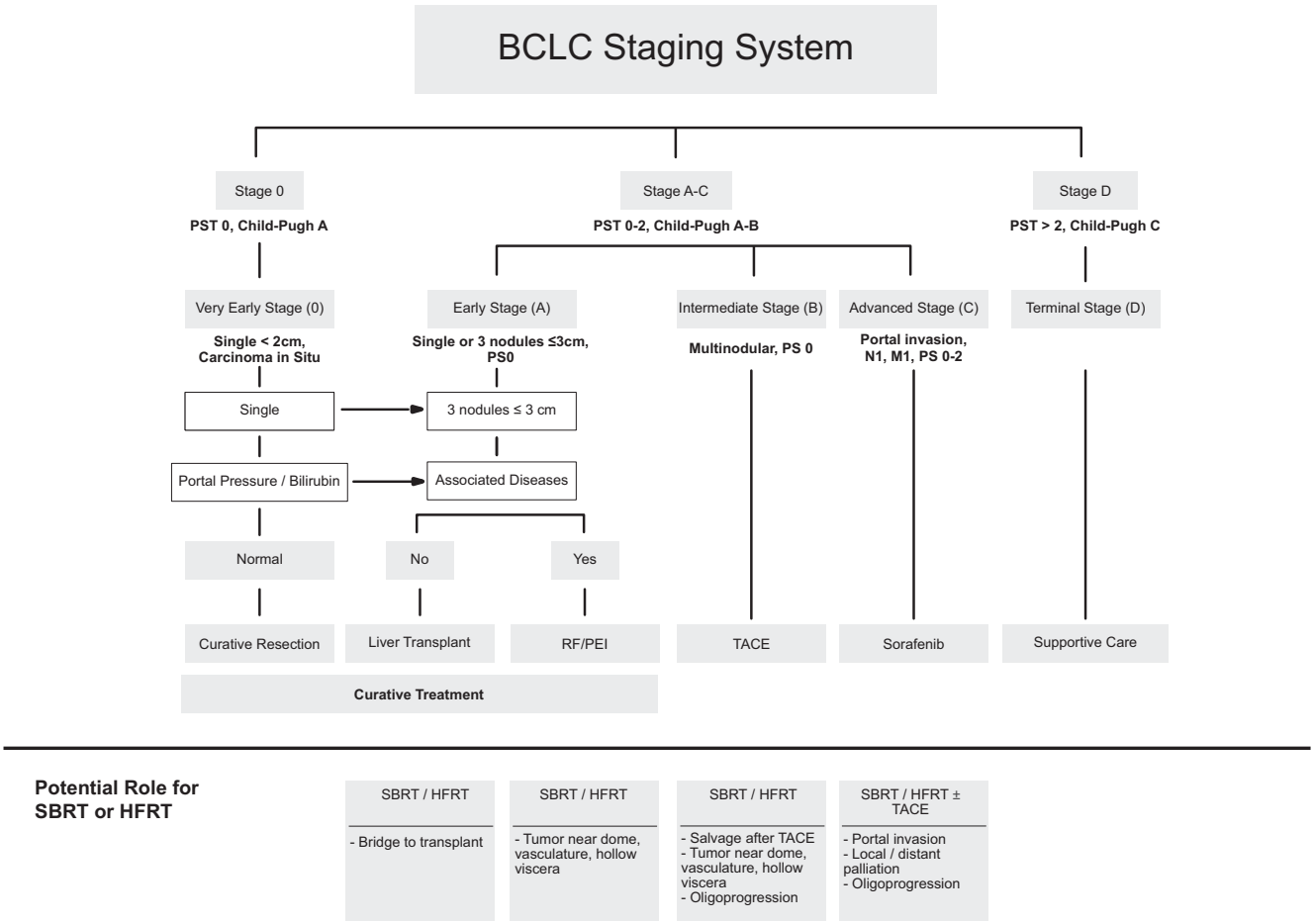

Figure 2. Barcelona Clinic Liver Cancer Staging and Treatment Strategy (top, adapted from Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis.* 1999;19:329-338, with permission). Potential role for SBRT or hypofractionated RT (bottom).