

ORIGINAL ARTICLE

Expanded use of aggressive therapies improves survival in early and intermediate hepatocellular carcinoma

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Abstract

Background: Despite the increasing annual incidence of hepatocellular carcinoma (HCC) in the USA, now estimated at 2.7 cases per 100 000 population, only a small proportion of patients receive treatment and 5-year survival rates range from 9% to 17%.

Objectives: The present study examines the effects of multimodal treatment on survival in a mixed-stage HCC cohort, focusing on the impact of radical therapy in patients with Barcelona Clinic Liver Cancer (BCLC) stage B disease.

Methods: A retrospective review of the medical records of 254 patients considered for HCC treatment between 2003 and 2011 at a large tertiary referral centre was conducted.

Results: A total of 195 (76.8%) patients were treated with a median of two liver-directed interventions. Median survival time was 16 months. In proportional hazards analysis, radiofrequency ablation (RFA) and resection were associated with significantly improved 1- and 5-year survival among patients with BCLC stage 0–A disease. In patients with BCLC stage B disease, RFA conferred a survival benefit at 1 year and resection was associated with significantly improved survival at 5 years.

Conclusions: As one of few studies to track the complete course of sequential HCC therapies, the findings of the present study suggest that HCC patients with intermediate-stage (BCLC stage B) disease may benefit from aggressive interventions not currently included in societal guidelines.

Received 12 September 2013; accepted 27 November 2013

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide; approximately 750 000 new cases are diagnosed and nearly as many attributable deaths occur per year.¹ In the USA, annual incidence increased by approximately 3.5% per year from 2001 to 2006, and is now 2.7 per 100 000 persons. This rate is expected to rise through the next

decade.^{2,3} In the USA, the major aetiological agents are chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection.² Excessive alcohol consumption and non-alcoholic steatohepatitis are also implicated, either as amplifiers of the effects of viral hepatitis or as independent risk factors.^{4,5} The United States Department of Veterans Affairs (VA) has been disproportionately affected by HCC, largely because of the high incidence of chronic HCV infection among VA patients (5.4%) compared with that in the general US population (1.8%). Currently, 173 000 VA patients are known to be chronically infected with HCV.⁶ Over the past decade, the VA has seen a five-fold increase in HCC cases.^{6–8}

In its earlier stages, HCC can be cured with aggressive therapies, but the optimal treatment strategy for patients in the intermediate

Funding: Veterans Affairs Merit Award Program (1I01-CX000295-01A1) and Veterans Affairs Hepatitis C Resource Center. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

stages of HCC has not been well established.^{3,9,10} Although treatment at any stage of HCC has been associated with survival benefits, only a small proportion of HCC patients receive any treatment over the course of their disease.^{3,11,12} Among US patients diagnosed with HCC between 1998 and 2008, 76% received no reported intervention. Although different treatment modalities are often employed sequentially, many studies report only on the first HCC therapy used and thus fail to capture the entire treatment experience.^{12–16} Other studies focus only on liver transplantation, the most curative intervention.^{17,18} Transplantation opportunities in HCC patients are limited by advanced stage at diagnosis, comorbid conditions, inadequate social support and constrained resources. There is a paucity of literature examining treatment patterns and outcomes in HCC patients in typical practice settings in which transplantation is not frequently employed.

Current societal guidelines recommend that only patients in the earliest stages of HCC should receive potentially curative HCC therapies, which typically include liver transplantation, hepatic resection and radiofrequency ablation (RFA).^{19,20} There is increasing evidence, however, in support of the extended use of some or all of these treatments in selected patients with intermediate-stage HCC.^{21–23} This retrospective medical records review was conducted to examine multimodal HCC treatment in a large tertiary referral veterans hospital. The study demonstrates that patients with both early- and intermediate-stage HCC can achieve a significant survival benefit from potentially curative interventions that are often reserved for early-stage patients.

Materials and methods

Ethics statement

This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and in a manner consistent with good clinical practice and applicable regulatory requirements.²⁴ A waiver of consent for the retrospective review of records for this specific study of HCC patient outcomes was obtained from the University of California San Francisco Institutional Review Board and approved by the San Francisco VA Medical Center (SFVAMC) Research and Development Committee.

Patient population and data collection

The study cohort included all previously untreated patients referred to SFVAMC for consideration for HCC treatment between April 2003 and April 2011. Patients in whom HCC was confirmed by histology, cytology or cross-sectional imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), were included. Those with equivocal cases of HCC or with heterogeneous tumour cells (i.e. HCC and cholangiocarcinoma) were excluded. The study end date was 28 February 2012.

Patient demographic characteristics and baseline clinical risk factors, including results of laboratory studies and tumour staging, were those recorded in the medical record on the date closest to the index visit. Infection with HBV, HCV or human

immunodeficiency virus (HIV) was confirmed using standard criteria. Alcohol abuse was defined as a longstanding history of excessive alcohol consumption (more than three standard drinks per day) or a history of alcohol-related medical complications.²⁵ Raw Model of End-stage Liver Disease (MELD) scores (i.e. without consideration for HCC exception points) and Child–Pugh classes were calculated from the medical record data according to standard methods.^{26–28} Using this information, tumours were staged by the investigators according to the Barcelona Clinic Liver Cancer (BCLC) classification system, which is widely accepted.^{20,29}

Treatment dates and modalities included those from the index visit to the study end date. Treatment decisions were made at multidisciplinary disease management conferences attended by hepatologists, surgeons, radiologists and medical oncologists, as guided by the National Comprehensive Cancer Network and the American Association for the Study of Liver Disease.^{19,20,29} In brief, surgical resection was considered for single tumours without vascular invasion or distant disease in the presence of adequate liver function. Radiofrequency ablation was most often used for single tumours of 3–5 cm in size in a favourable location in patients who did not fulfil the resection criteria. Other liver-directed therapies, henceforth termed 'locoregional therapies' (LRTs), include transarterial (chemo)embolization [TA(C)E], microwave ablation (MWA) and percutaneous ethanol injection (PEI). Locoregional therapies were used to achieve initial control of tumours prior to radical therapy or solely as palliative treatment. Transarterial (chemo)embolization was most often used in patients with several small tumours or impaired liver function. Percutaneous ethanol injection was generally only used for tumours of <3 cm in size.

Further interventions (other than liver transplant) were performed most commonly for recurrent HCC, although some lesions required serial therapies. Repeat contrast CT or MRI was obtained 1–3 months after each treatment, and then serially at 3–6-month intervals. Guided by the consensus in the literature, patients were grouped into one of five treatment groups in declining order of efficacy, based on the most efficacious treatment they had ever received: (i) liver transplantation; (ii) surgical resection; (iii) RFA; (iv) LRT, and (v) no procedural intervention. (Patients who received chemotherapy only and those who received no treatment were combined for analytic purposes, but are described separately in Table 3.)

Major outcomes

The major outcomes explored in this study were: (i) median survival time; (ii) overall survival by BCLC stage at the index visit, and (iii) 1-year and 5-year hazard ratios (HRs) for survival, stratified by BCLC stage (0–A and B), for the most efficacious treatment modality used.

Data sources

Study data were abstracted from the VA's comprehensive electronic medical record system by two investigators, using a stand-

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