



Diagnosis and management of hepatocellular carcinoma: results of a consensus meeting of The Ottawa Hospital Cancer Centre

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ABSTRACT

Hepatocellular carcinoma (HCC) is an uncommon tumour, but its incidence is increasing in Canada and elsewhere. Currently, there are no Canadian recommendations for diagnosis and treatment of HCC, and possible options may have regional limitations. A consensus symposium was held in the Ottawa region to consider current diagnostic and management options for HCC. These recommendations were developed:

- Diagnosis—with adequate imaging, a biopsy is not required pre-surgery, but is required before the start of systemic therapy; lesions smaller than 1 cm should be followed and not biopsied; repeat biopsies should be core tissue biopsies; magnetic resonance imaging is preferred, but triphasic computed tomography imaging can be useful
- Resection—recommended for localized HCC
- Radiofrequency ablation—recommended for unresectable or non-transplantable HCC; should not be performed in the presence of ascites
- Trans-arterial chemoembolization (TACE)—doxorubicin with lipiodol is the agent of choice; trans-catheter embolization is an alternative for patients if TACE is not tolerated or is contraindicated
- Medical management—first-line sorafenib should be considered the standard of care
- Transplantation—suitable patients meeting Milan criteria should be assessed for a graft regardless of other treatments offered

The authors feel that the recommendations from this consensus symposium may be of interest to other regions in Canada.

KEY WORDS

HCC, hepatoma, treatment, regional consensus guideline

1. INTRODUCTION

A consensus symposium on hepatocellular carcinoma (HCC) was held in Ottawa, Ontario, in September 2008 to consider current diagnostic and therapeutic options for HCC. The framework of these deliberations is likely to be of interest in other parts of Canada where variability in access to imaging, pathology testing, and treatment expertise make it helpful to develop a regional approach. An approach to standards of cancer care is considered appropriate if it is in the context of local resources and needs.

2. EPIDEMIOLOGY AND PATHOGENESIS

Worldwide, HCC is the sixth most common cancer and the third leading cause of cancer-related death¹. The incidence of HCC varies widely geographically because of differences in the major causative factors. The most dominant risk factor for development of HCC is underlying liver cirrhosis². Regardless of cirrhotic causation, HCC develops 80%–90% of the time in patients who have cirrhosis². Primary viral infection with the hepatitis B or C virus and high alcohol intake are associated with the highest risk of developing cirrhosis and thus HCC³. Most recently, non-alcoholic fatty liver disease (NAFLD)—and associated obesity and diabetes—has emerged as a risk factor for HCC^{4,5}.

Asia and sub-Saharan Africa have the highest incidences of HCC—attributable to the high rate of chronic hepatitis B viral infection⁶. North America, Western Europe, and Australia are considered low-incidence regions, although their incidence of HCC is rising. In the United States, the rate of HCC has doubled since the start of the 1990s, with the age-specific incidence progressively shifting toward a younger population^{4,7}. This increase in the rate of HCC has been attributed to the large pool of people with longstanding chronic hepatitis C infection contracted either domestically or in areas in which hepatitis C is endemic, and to the increased prevalence of NAFLD^{4,8–10}.

If diagnosed in its early stages, HCC is amenable to potentially curative treatment with surgery (resection with partial hepatectomy or liver transplantation) and locoregional therapy [radiofrequency ablation, trans-catheter embolization (TAE), trans-arterial chemoembolization (TACE)]. However, for patients with advanced—that is, unresectable—disease, the goal has been palliative treatment to prolong survival and control symptoms.

3. PATHOLOGY DIAGNOSIS OF HCC

A high level of serum alpha fetoprotein (>400 ng/mL) in the presence of a solid hypervascular liver lesion is highly suggestive of HCC. Although differentiating regenerative nodules from other nodules in the liver remains a challenge, advances in cross-sectional imaging have improved the characterization of focal liver lesions, greatly reducing the requirement for a liver biopsy. Still, cross-sectional imaging remains inaccurate for diagnosing small malignant tumours, especially tumours less than 2 cm in diameter. If the diagnosis remains in question, biopsy may be required to make a definitive diagnosis. In such cases, positive results of a fine-needle aspiration (FNA) biopsy are helpful; however, negative FNA results should be interpreted with caution. Patients with negative FNA biopsy should undergo a second biopsy or repeated computed tomography (CT) or magnetic resonance imaging (MRI) investigations, or both.

Compared with FNA, core biopsy may provide more pathologic information because, in addition to cytologic features, architecture can be evaluated. The cells of HCC grow in a pattern that mimics normal liver, most often producing a trabecular pattern with thickened cords (more than 3 cells) separated by vascular sinusoids. Less common patterns are pseudoglandular, solid, scirrhous, and HCC with clear cells. Fibrolamellar HCC occurs mostly in young people and shows abundant intercellular fibrosis and pleomorphic nuclei. Grading of HCC can be done on the basis of nuclear features alone, from grade 1 (well differentiated) to grade 4 (poorly differentiated).

On FNA and small core biopsy, a diagnosis of high-grade HCC is usually straightforward; however, well-differentiated HCC is difficult to differentiate from adenoma or regenerative and dysplastic nodules. The cells of well-differentiated HCC are very similar to those of normal liver, showing only minimal nuclear irregularity, a slightly higher N:C ratio, and abundant eosinophilic cytoplasm. Numerous currently available immunostains provide valuable diagnostic information to assist pathologists in the diagnosis of difficult cases. These include, but are not limited to, hepatocyte paraffin 1 (which stains the cytoplasm of hepatocytes in 90% of HCCs), alpha fetoprotein (positive in 40%–50% of HCCs), CD34 and CD10 (which stain diffusely the endothelial cells surrounding the trabeculae of HCCs), and polyclonal carcinoembryonic

antigen (which stains the bile canaliculi, in both normal liver and HCC). The most recent antibody added to the panel is glypican-3 (GPC3), a membrane-bound proteoglycan that is overexpressed in HCC, but undetectable in normal liver or other primary benign or malignant hepatic lesions. In a recent study, GPC3 analysis in cytology material demonstrated a sensitivity of 83% and a specificity of 96% for detecting HCC¹¹ as compared with adenoma.

Selected immunostains, in addition to the morphologic and clinical features, can be very helpful in establishing the diagnosis of HCC in difficult cases.

3.1 Recommendations

If a patient presents with classical imaging and is a candidate for surgery, then biopsy is not required.

If a patient has unresectable HCC and is being considered for systemic therapy, then biopsy is required.

A lesion smaller than 1 cm should not be biopsied, but should be followed at 3-month intervals (changing to 6-month intervals if the lesion remains stable).

Repeat biopsies should be core tissue biopsies, rather than FNAs.

4. DIAGNOSTIC IMAGING IN HCC

Imaging has numerous roles in HCC, including screening, diagnosis, staging, and follow-up. A recently published systematic review used a computerized decision-analytic model to compare various surveillance strategies for early diagnosis of HCC¹². Based on the assumptions used in the model, the most effective surveillance strategy is a combination of testing for alpha fetoprotein and ultrasound imaging performed every 6 months. Compared with no surveillance, this strategy was estimated to more than triple the number of people with operable HCC tumours at time of diagnosis and to almost halve the number of deaths from HCC. The cost-effectiveness of various surveillance strategies for HCC varies depending on the causation involved. Screening for HCC with triphasic CT is a cost-effective strategy in transplant-eligible patients with cirrhosis secondary to chronic hepatitis C viral infection¹³.

Diagnosis of HCC depends heavily on imaging characteristics; biopsy is generally not required before surgery. Ultrasound plays a key role in the detection of HCC, being widely available, relatively inexpensive and easy to perform, but of low sensitivity for identifying additional small nodules¹⁴. A 2006 systematic review and meta-analysis pooled data from fourteen ultrasound studies, and found sensitivity to be 60%, and specificity to be 97%¹⁵. In the same systematic review, pooled data from ten helical CT studies indicated that CT has better sensitivity than ultrasound (68% vs. 60%) and similar specificity (93%). Of three imaging techniques, MRI had the best sensitivity at 81% and a similar specificity of 85% (pooled data from nine MRI studies)¹⁵.

In addition to assisting with the detection of hepatic metastases, intraoperative ultrasound (IOUS) has evolved into a valuable tool for a final evaluation of operability during surgical exploration. In a study by Silberhumer *et al.* that compared liver imaging with histopathology results, the sensitivity of IOUS was 92%–99%, and surgical strategy was changed based on the IOUS results in 10% of cases¹⁶. Thus, IOUS is highly sensitive and remains a mandatory tool for evaluating patients undergoing liver surgery.

4.1 Recommendations

The ideal imaging modality is MRI, which should be performed as early in the disease course as possible.

Triphasic CT scanning can be useful for preoperative planning.

5. STAGING

To date, no single staging system for HCC has been universally accepted. The most widely accepted staging systems include tumour–node–metastasis (TNM), Okuda, the Cancer of the Liver Italian Program score, and the Barcelona Clinic Liver Cancer (BCLC) staging classification.

Most of these models describe the severity of the underlying liver disease, the size of the tumour, extension of the tumour into adjacent structures, and the presence of metastases. The BCLC classification

uses parameters related to tumour stage, liver function status, physical status, and cancer-related symptoms, and it brings those four parameters into a treatment algorithm (Figure 1). In comparative studies, BCLC was shown to be a more superior prognostic model in patients undergoing surgical therapy and the best suited for treatment guidance in patients who could benefit from curative therapies^{18–22}.

5.1 Recommendations

Multiple staging classification systems for HCC are accepted.

The BCLC classification has been shown to be a superior for predicting prognosis and for guiding therapy in early-stage disease.

6. ROLE OF RESECTION IN HCC

Hepatic resection is widely accepted as the primary treatment for patients with localized HCC, even in selected patients with cirrhosis. Accordingly, estimates suggest that only 15%–30% of patients with HCC are candidates for resection at the time of presentation²³. As a result of advances in patient selection and surgical resection procedures, particularly in cirrhotic patients, the perioperative mortality in HCC is below 3%, and 5-year survival rates are at least 50%^{24,25}. This 5-year survival represents a significant improvement from earlier years, when

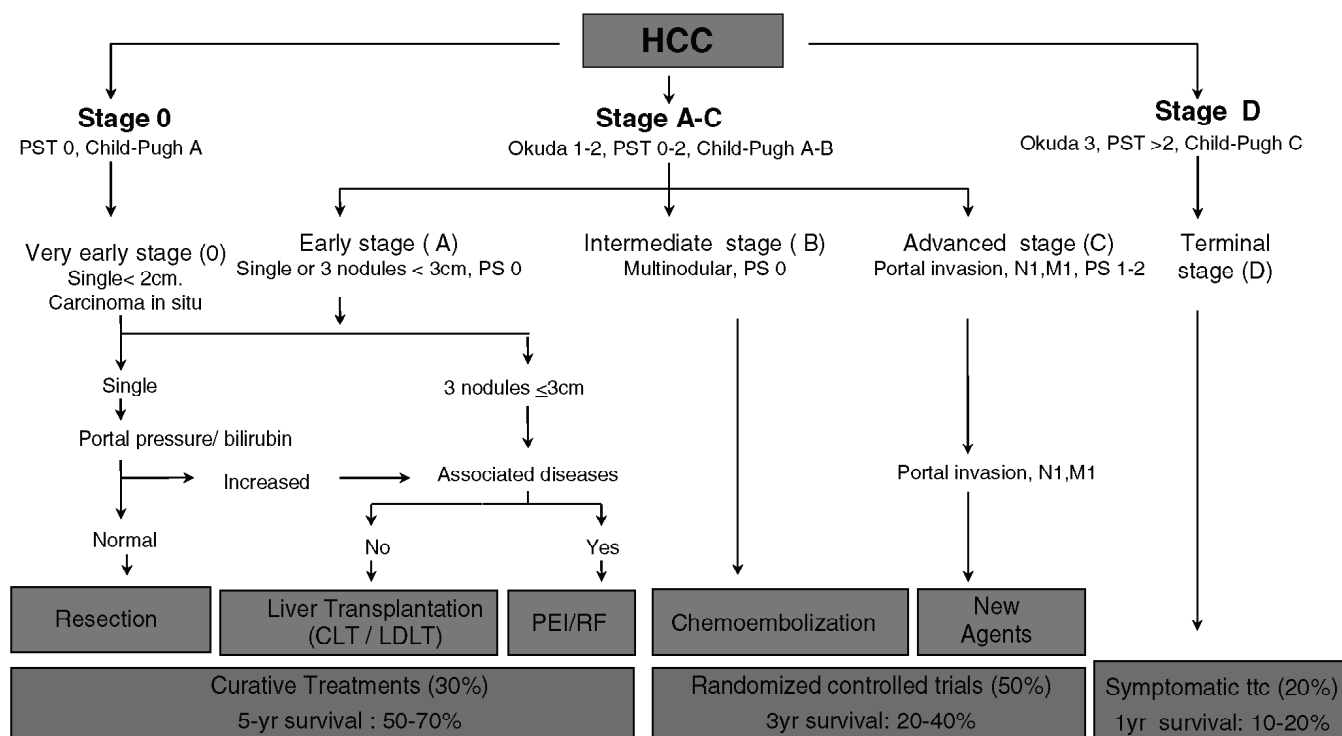


FIGURE 1 Barcelona Clinic Liver Cancer staging and treatment schedule. PST = performance status test. Adapted from Llovet *et al.* 2003¹⁷.

5-year survival for patients undergoing hepatectomy for HCC was 12%–20%²⁶. Long-term survival remains unsatisfactory, however, because of the high incidence of tumour recurrence (the main cause of poor prognosis), which ranges from 60% to 100% at 5 years²⁷.

Numerous studies have evaluated the factors that could improve surgical outcomes and disease-free survival. Specifically, these studies retrospectively analyzed patients with liver resection for HCC to glean information on the prognostic values of clinical, surgical, pathologic, and biologic factors affecting long-term outcome and intrahepatic recurrence^{26–31}. For example, in a retrospective analysis, Ramacciato *et al.* reported that viral cause of cirrhosis, presence of multiple nodules, and vascular invasion negatively affected recurrence rate and long-term survival³⁰. Similarly, for 320 patients with HCC who underwent hepatectomy in Japan, Taniai *et al.*³¹ reported an overall 5-year disease-free survival rate of 45.0% in the group with smaller HCCs and 33.6% in the group with HCCs of diameter 10 cm or greater. This finding led the authors to suggest that cirrhotic patients with huge HCCs (that is, ≥ 10 cm) and both macrovascular invasion and multiple tumours may not be appropriate candidates for hepatic resection³¹. In general, the conclusion of the various studies has been that selection of ideal candidates for surgical resection involves adequate assessment of a number of factors, including liver function (that is, Child–Pugh stage) and level of tumour extension.

6.1 Recommendation

Hepatic resection should be considered the primary treatment for patients with localized HCC.

7. ROLE OF LIVER TRANSPLANT IN HCC

By resection of the whole liver, liver transplantation has the advantage of treating the underlying liver disease and removing any undiagnosed HCC. Recent studies have demonstrated excellent outcomes in carefully selected patients with limited HCC disease who were treated with liver transplantation. In a landmark study, Mazzaferro *et al.* found that patients with small, unresectable tumours had recurrence-free survival rates similar to those in patients undergoing liver transplantation for non-malignant liver disease³². Their results formed the basis of the Milan criteria for liver transplantation, which advocates liver grafts for potential recipients who have 1 lesion 5 cm or smaller, or up to 3 lesions each 3 cm or smaller.

No prospective randomized controlled trials (RCTs) have compared hepatic resection and liver transplantation for patients with HCC. In a 2002 review, Wong summarized the results of trials that retrospectively compared liver resection with transplantation in patients with HCC³³. In eight trials

published between 1995 and 2001, the 5-year survival was 35%–51% for liver resection, compared with 60%–72% for liver transplantation. In nine studies published between 1991 and 2001, the recurrence rates were 19%–65% for liver resection, compared with 0%–43% for liver transplantation. Although the studies varied with regard to length of follow-up, each individual study demonstrated a lower recurrence rate with transplantation.

7.1 Recommendation

Patients with HCC who meet the Milan criteria and who are otherwise deemed candidates for transplantation should be assessed for transplantation regardless of other treatments offered.

8. ROLE OF RADIOFREQUENCY ABLATION IN HCC

Radiofrequency ablation (RFA) has rapidly become one of the treatments of choice for patients with HCC who are not candidates for resection or transplantation. In patients with HCC awaiting liver transplantation, RFA has also been evaluated as bridge therapy, and in patients with early, non-surgical HCC, RFA is considered more effective than percutaneous ethanol injection with respect to local recurrence and overall and disease-free survival^{34,35}. A recent RCT compared RFA and surgical resection in patients with a solitary resectable HCC ≤ 5 cm and found similar overall and disease-free survival rates, suggesting that RFA may be as effective as resection in this patient cohort³⁶. Percutaneous ethanol injections are also a local control option that may be safer than RFA in tumours near major blood vessels³⁷.

Unfortunately, local recurrence at the treatment site after RFA is not an uncommon observation. In a retrospective study, Lam *et al.* found that, at 2 years' median follow-up, risk of local recurrence was 13%, and tumour size greater than 2.5 cm was the only independent risk factor for local recurrence. No notable difference in overall survival was evident between patients with and without local recurrence³⁸.

Major complications with RFA are thought to be rare and mostly self-limiting. In a recent study of 218 patients treated with RFA for a single small HCC, the rate of major complications was 1.8%³⁹.

8.1 Recommendations

In the presence of ascites, RFA increases the risk of seeding and should not be performed. Consider drainage of the ascites before RFA.

Needle biopsy before RFA increases the risk of seeding and should be avoided; however, it may be performed as part of the RFA procedure.

Imaging by CT post RFA must be labelled as such and assigned to an appropriate (RFA-experienced) radiologist.

Note: In Ottawa, the first follow-up CT imaging is done 28 days following the RFA procedure to avoid interpretation errors from immediate post-RFA inflammatory changes.

9. ROLE OF REGIONAL CHEMOTHERAPY IN THE MANAGEMENT OF HCC

The most widely used primary treatment for patients with unresectable HCC is TAE to induce tumour necrosis. Materials commonly used to induce tumour-vessel embolization include microspheres and Gelfoam (Pfizer, New York, NY, U.S.A.) particles. The TACE procedure combines selective embolization of tumour vessels with administration of chemotherapeutic drugs including doxorubicin, cisplatin, and mitomycin, alone or in combination. Lipiodol is often also added to the chemoembolization region to enhance the antitumour effect of the drugs by prolonging their contact with tumour cells. For patients with unresectable primary liver cancer, TACE is intended as a palliative treatment; for patients awaiting liver transplantation, it is a bridging therapy. More recently, small trials have investigated the utility of using doxorubicin beads in the TACE procedure⁴⁰.

Two meta-analyses demonstrated that TACE significantly improves overall survival in individuals with unresectable hepatocarcinoma^{41,42}, although treatment with tamoxifen did not modify the survival of patients with advanced disease⁴². A third meta-analysis failed to demonstrate a significant survival advantage for therapeutic embolization over supportive care alone in patients with unresectable HCC⁴³. Geschwind and colleagues concluded that existing survival data from RCTs are of poor quality, and the low numbers of patients in these trials eliminate the possibility of drawing meaningful conclusions regarding the effect of TACE on patient survival⁴³.

The role of TACE remains controversial, with uncertain efficacy when compared with TAE alone in patients with inoperable disease. Marelli *et al.* performed a systematic review to evaluate whether embolization alone confers a survival advantage over TACE in patients with HCC. Although a meta-analysis of nine RCTs confirmed that TACE improves survival, a meta-analysis of three RCTs comparing TACE with TAE ($n = 412$) failed to demonstrate a survival difference between the two techniques⁴⁴. Marelli and colleagues concluded that further trials comparing these treatments are needed to determine unequivocally if TACE provides a survival advantage over TAE alone⁴⁴.

9.1 Recommendations

If TACE is used, doxorubicin (with lipiodol) is the chemotherapeutic agent of choice.

Bland embolization may be the treatment modality of choice, especially when TACE is contraindicated or not tolerated.

The role of embolization should not depend on sorafenib (localized versus systemic therapy).

Most patients with HCC present with advanced disease; only 10%–20% of patients are candidates for curative surgery. For patients with advanced disease, the prognosis is poor, with a median survival of only 4 months⁴⁵. Patients classified BCLC stage C are candidates for systemic therapy; those classified stage D, for palliative care only²⁰.

In patients not eligible for surgery or declining liver surgery, systemic treatment options are available, but have traditionally been limited and minimally effective⁴⁶. In 2007, however, the antitumour agent sorafenib, widely used for the treatment of primary kidney carcinoma⁴⁷, was found to produce a clinically meaningful improvement in survival in patients with advanced HCC⁴⁸.

Sorafenib is an orally active multikinase inhibitor with activity against tyrosine and serine/threonine kinases, key components in hepatocarcinogenesis^{49,50}. It also exerts a direct antitumour effect by *raf* kinase inhibition and an anti-angiogenic effect by vascular endothelial growth factor receptor inhibition.

In the randomized double-blind placebo-controlled phase III SHARP trial, 400 mg of oral sorafenib administered twice daily significantly improved survival by 3 months in patients with advanced HCC ($n = 299$; placebo group, $n = 303$). In addition, the median time to disease progression was significantly longer in patients receiving sorafenib than in those receiving placebo (5.5 months vs. 2.8 months). Treatment with sorafenib twice daily was generally well tolerated with a manageable adverse event profile⁴⁸. The SHARP trial was stopped at the second planned interim analysis because of the survival advantage favouring the sorafenib arm. Sorafenib was also shown to be effective in patients from the Asia-Pacific region⁵¹. Sorafenib was subsequently approved by both the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of patients with advanced HCC⁴⁶. Current U.S. treatment guidelines recommend sorafenib as a first-line treatment option in patients with unresectable HCC who are classified Child-Pugh A or B⁴⁶.

Recently, combination therapy with sorafenib and doxorubicin has shown promise for the treatment of patients with advanced HCC. The randomized double-blind phase II clinical trial of this therapy ($n = 96$) demonstrated that oral sorafenib (400 mg) twice daily combined with intravenous doxorubicin 60 mg/m² every 21 days has potential in patients with advanced HCC⁵².

9.2 Recommendation

First-line therapy with sorafenib should be considered the standard-of-care treatment for advanced HCC.

Patients should still be enrolled in clinical trials, where available.

10. SUMMARY

Hepatocellular carcinoma is a malignancy that affects a large number of patients, and the incidence of this disease can be expected to increase in Canada and throughout the world. Treatment and diagnostic changes have improved prognosis for many patients with HCC. As seen in the present paper, the optimal method for improving the care of these patients is multidisciplinary collaboration. Improvements in therapies such as hepatic resection and hepatic transplantation have improved the cure rate of this disease. As well, advances in the medical treatment of HCC and in interventional techniques such as RFA have significantly improved the palliative treatment of HCC.

11. CONFLICT OF INTEREST DISCLOSURE

This consensus meeting was funded by an unrestricted educational grant from Bayer.

12. ACKNOWLEDGMENTS

The authors thank Isabella Steffensen for editorial assistance.

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