Prognosis in the early stages of hepatocellular carcinoma: Predicting outcomes and properly selecting patients for curative options

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Hepatocellular carcinoma (HCC) is the fifth most common malignancy in men and the seventh most common cancer in women (1). In 2008, more than 750,000 new cases were diagnosed worldwide (1). Although 85% of HCC cases occur in developing countries, the incidence of HCC is increasing in many western countries including Canada. Between 1996 and 2000, the incidence rates of HCC in Canada were estimated to be 10.7 per 100,000 population in men, and 3.2 per 100,000 in women (2). These rates are projected to increase to 18.5 per 100,000 in men, and 4.1 per 100,000 in women in 2011 to 2015 (2). This represents nearly 10,000 new cases of HCC in Canada during this time period. Unfortunately, HCC is the third leading cause of cancer-related mortality worldwide, owing to a very high mortality to incidence ratio of 0.93 (1). HCC will continue to have a poor prognosis unless it is diagnosed at an early stage. Providing appropriate screening to high-risk individuals is essential to identify patients at early stages of HCC in which the potentially curative therapies of surgical resection, radiofrequency ablation (RFA) and liver transplantation (LT) can be offered (3).

In the current issue of The Canadian Journal of Gastroenterology (pages 485-491), Ko et al (4) explore prognostic factors in Taiwanese patients undergoing surgical resection. They restricted their retrospective analysis to 140 subjects with stage I (solitary tumour without vascular invasion) or stage II disease (solitary tumour with vascular invasion or multiple tumours all ≤5 cm in size) according to the TNM staging system. They reported an excellent five-year overall survival rate of 79% and confirmed the ability of the TNM system to correctly stratify the prognosis of early stage patients (five-year survival in stage I was 82% versus 72% in stage II patients). On multivariate analysis, stage II disease conferred a 78% increased risk of tumour recurrence compared with stage I (HR 1.78 [95% CI 1.06 to 2.99]; P=0.03) (4). Therefore, by definition, vascular invasion and/or multifocality (which define stage II) are important prognostic factors following surgical resection. Many other studies have confirmed these findings. An analysis of the Surveillance, Epidemiology, and End Results (SEER) database examined prognostic factors in 788 American patients undergoing surgical resection for early stage HCC in which the potentially curative therapies of surgical resection, radiofrequency ablation (RFA) and liver transplantation (LT) can be offered (3).

Patients who are not candidates for surgical resection due to liver failure or portal hypertension may undergo RFA as an alternative treatment. Although tumours up to 5 cm in size can be targeted with RFA, the single most important predictor of failed therapy or recurrent disease is tumour size. A study of 273 patients from Hong Kong (11) found that tumour size >2 cm (HR 1.51), multifocality (HR 1.51), and microvascular invasion (MVI, HR 1.44) were independent predictors of increased mortality. Patients with none of these factors had a five-year survival rate of 55%; this fell to 42% with one factor and only 29% if two or three factors were present (5). In the study by Ko et al (4), the only other significant independent predictor of recurrence was older age. Because this study included only patients with HCC related to viral hepatitis (54% had hepatitis B and 46% had hepatitis C), and only 30% received antiviral therapy, the effect of age may actually represent the impact of longer durations of chronic viral hepatitis on the development of cirrhosis and risk of recurrence.

On multivariate survival analysis, Ko et al determined that male sex and low albumin level were significantly associated with increased mortality following resection. We know that men are 2.4 times more likely than women to develop HCC (1), and the study by Ko et al suggests that males are three times more likely than women to die following surgical resection of early stage HCC. The significance of albumin lies in the importance of preoperative liver function as a predictor of outcomes following surgical resection. In their study, Ko et al reported that approximately two-thirds of patients had cirrhosis and the vast majority of subjects were Child-Pugh class A. The Barcelona Clinic Liver Cancer (BCLC) group has determined that bilirubin elevation (>1 mg/dL [>17 µmol/L]) and/or the presence of portal hypertension (defined clinically as splenomegaly, platelets <100×10^9/L or presence of esophageal varices, or as a hepatic venous pressure gradient ≥10 mmHg), can be used to further stratify the outcomes of Child-Pugh class A patients (6). In their hands, patients with normal bilirubin levels and no portal hypertension had a five-year survival rate of 74% following surgical resection of HCC. In the presence of portal hypertension, the five-year survival rate fell to approximately 50% and, if patients had both portal hypertension and elevated bilirubin levels, this fell to approximately 25% (6). Therefore, bilirubin level and portal hypertension have been incorporated into the BCLC staging system (3) and the Alberta HCC Algorithm (7). In the study by Ko et al, 96% of subjects were Child-Pugh class A with a mean bilirubin level of 10.6 µmol/L (interquartile range 7.9 µmol/L to 15.0 µmol/L); however, no information regarding the presence or absence of portal hypertension was provided. The authors did determine that for each 10 g/L increase in albumin, mortality decreased by 45% [HR 0.40 [95% CI 0.19 to 0.85]; P=0.0188] (4). Recently, another group from Japan found that low albumin and tumour multifocality were independent risk factors for tumour recurrence following resection or RFA (8). Our group also demonstrated the importance of albumin as a predictor of survival in patients awaiting LT in the United States (9). Adding albumin to the Model for End-stage Liver Disease (MELD) or the MELD–sodium, to create a new five-variable MELD, significantly improved the ability of the model to predict short-term mortality in cirrhotic patients (9).

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The long-term outcomes of LT for HCC are excellent, typically with recurrence rates of <15% in patients selected using the Milan criteria (single tumour ≤5 cm or up to three tumours all ≤3 cm) (12). In the absence of randomized controlled trials, it is difficult to compare outcomes in patients undergoing surgical resection versus LT (6). Patients who undergo resection tend to be older and have larger tumours but with more preserved liver function (usually Child-Pugh class A), whereas LT recipients are younger, with smaller tumours but more advanced cirrhosis (often Child-Pugh class B or C) (6). A recent evaluation of 143 patients undergoing LT for HCC in Alberta (7), demonstrated a five-year overall survival rate of 74%, despite many of these patients being beyond the Milan criteria.

Similar to surgical resection, the presence of MVI is a very important predictor of tumour recurrence and subsequent poor outcomes following LT. On developing a pathological score to predict recurrence following LT, the University of Western Ontario (London, Ontario) found that MVI was the strongest predictor of HCC recurrence based on explant pathology (13). Although MVI is present in approximately one-third of early stage cancers, current imaging modalities are too insensitive to accurately identify this histological finding before LT. Therefore, we are left with using tumour size and/or multifocality to predict the presence of MVI to properly select patients for LT. A recent retrospective analysis of the Metro-Ticket Registry (14) found that MVI was present in 31 of 187 (17%) patients within the Milan criteria, and 287 of 572 (50%) patients beyond these criteria (14). MVI, the strongest predictor of post-transplant survival, was associated with a twofold risk of death during follow-up (14). This led to the development of separate predictive nomograms for post-LT survival (with and without MVI) based on tumour number and size of the largest lesion (14).

However, it appears that size, rather than multifocality, is a more important predictor of subsequent recurrence and death after LT for HCC. A recent meta-analysis (15) determined that the largest diameter of a tumour nodule or the total sum of all nodules affected disease-free and overall survival after LT. Patients who had a total sum of tumour diameter >10 cm (note that the maximum for the Milan criteria is 3 cm + 3 cm + 3 cm = 9 cm), had an HR for death of 4.59 (95% CI 1.26 to 16.79); however, the tumour number (HR 1.09 [95% CI 0.88 to 1.34]) and multiple versus single (HR 1.23 [95% CI 1.00 to 1.53]) were not significant predictors of recurrence or overall survival (15). An analysis based on the Scientific Registry of Transplant Recipients (SRTR) of 6478 LT procedures performed for HCC in the United States (16), showed that a total tumour volume (TTV) of >115 cm$^3$ and alpha-fetoprotein (AFP) level of >400 ng/mL were independent predictors of survival after LT. Patients within these criteria had a four-year overall survival post-LT of 60%, but if either factor was present, the three-year patient survival rate fell below 50% (16). Because TTV (calculated as 4/3 π r$^3$) is driven by the radius (r) of the largest lesion, TTV does a good job at reflecting the importance of size versus multifocality. For example, a single lesion of 6 cm has a TTV of 113 cm$^3$, whereas three lesions of 4 cm each equates to a TTV of 101 cm$^3$, and a patient with five lesions of 2 cm each has a TTV of only 21 cm$^3$. AFP level was also found to be an independent predictor of recurrence (AFP ≥100 ng/mL, HR 2.01) in a time-dependent analysis of Japanese patients undergoing resection or RFA (8). In the study by Ko et al, stage II patients were significantly more likely to have an AFP level >400 ng/mL (29% versus 11%), reflecting that AFP may be a reasonable marker of MVI or more aggressive tumour histology because stage II patients were also more likely to have poor to moderate differentiated tumours (4). We have now adopted TTV >115 cm$^3$ and AFP >400 ng/mL as the new listing criteria for LT in Alberta (7).

The University of Toronto (Toronto, Ontario) has recently published their experience of expanding the Milan criteria using a biopsy to exclude patients with poorly differentiated tumours from LT (17). They reported excellent outcomes, including a five-year overall survival rate of 70% in 105 patients beyond the Milan criteria, using a protocol that included aggressive locoregional therapy while patients awaited LT (17). In their series, the size or total number of tumours were not predictors of recurrence; however, AFP >400 ng/mL at the time of LT was associated with poorer disease-free survival (HR 2.3 [P=0.031]) (17). In the future, gene expression signatures on biopsy or resection specimens may improve the diagnosis of MVI and further guide selection for LT or the design of clinical trials evaluating adjuvant therapy after curative treatment (18). To date, unfortunately, no adjuvant therapy has been shown to be effective in reducing the risk of HCC recurrence. However, we await the results of the Sorafenib as Adjuvant Treatment in the Prevention Of Recurrence of Hepatocellular Carcinoma (STORM) trial evaluating the role of sorafenib as adjuvant therapy following curative intent resection or RFA.

Identification of poor prognostic factors may prompt us to perform enhanced surveillance for recurrence following surgical resection. Unfortunately, one of the major criticisms of the Ko et al article is that they do not describe how patients were followed after surgery to monitor for recurrence. The National Comprehensive Cancer Network (available online at www.nccn.org) has proposed imaging every three to six months for two years, and annually thereafter. Certainly, the risk for recurrence is highest in the first two years after therapy, accounting for one-half of the recurrences in the Ko et al study. However, because it is recommended that all patients who are at increased risk for HCC undergo ultrasound every six months for screening (6), I believe that surveillance imaging should be intensified in patients who have undergone surgical resection or ablation, in which the risk of recurrence may exceed 70% within five years (5). Therefore, in Calgary (Alberta) we perform magnetic resonance imaging, alternating with contrast-enhanced ultrasound every three months for the first two years after surgical resection or RFA, after which these tests are alternated every six months.

**SUMMARY**

Selection of patients for curative treatment options for HCC depends on tumour bulk (size, number or volume) and liver function (as measured by Child-Pugh score, bilirubin and albumin levels, and portal hypertension). MVI is an important predictor of recurrence in early stage HCC but, unfortunately, is often only available on review of the surgical pathology after the therapy has already been performed. Patients can be transplanted beyond the Milan criteria with good outcomes, although biopsy and/or AFP should be used to exclude patients at the highest risk of recurrence.

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**REFERENCES**


