W Bautista, J Klein, S Cuvelier, et al. Cancer stem cell invasion of the hepatic microvasculature as a predictor of tumour recurrence following surgical resection in adult patients with hepatocellular carcinoma. Can J Gastroenterol Hepatol 2015;29(8):409.

To the Editor:

Tumour invasion of the hepatic microvasculature is considered to be an important predictor of recurrence following surgical resection for hepatocellular carcinoma (HCC) (1). Recently, cancer stem cells (CSCs) have been implicated in the process of tumour invasion (2). Thus, in the present study, we hypothesized that CSCs would be present in HCC tissues invading the hepatic microvasculature and that the prevalence of CSCs within the invading tissue would correlate with the development and/or time to tumour recurrence (TTR) postresection. The medical records of nine adult patients who had undergone surgical resections for nonmetastatic HCC and were reported to have histological evidence of microvasculature invasion were reviewed. No patient had received previous local-regional, systemic or adjuvant tumour therapy. CSCs were identified in paraffin-embedded tissues using EpCAM positive immunohistochemical staining as described previously (3). CD31 staining served to identify vascular endothelial cells. A CSC-invasion index (CSC-II) was calculated by dividing the percent of CSCs within tumour tissue invading the hepatic microvasculature by the percent of CSCs within the remaining nonvasculature invading tumour tissue. Postresection tumour recurrences were detected by computed tomography (CT)/magnetic resonance imaging of the abdomen and x-ray/CT of the chest every six months or earlier if dictated by clinical suspicion. The study was approved by the Health Research Ethics Boards at the University of Manitoba (Winnipeg, Manitoba).

The findings of the study are provided in Table 1. CSCs were present in all tumour tissues invading the hepatic microvasculature. CSCs were also present in the remaining, noninvading tumour tissue. The mean percent of CSCs within tissues invading the microvasculature was 59.9±18.9% (range 29% to 93%) and 52.6±18.2% (range 26% to 79%) in the remaining tumour tissues. The mean calculated CSC-II was 1.21±0.36 (range 0.557 to 1.846). Tumour recurrences developed in all nine subjects. The mean TTR was 21.3±15.4 months (range 3.6 to 48.3 months). There were no correlations between TTRs and the percent of CSCs within tumour tissue invading the microvasculature (r=0.23), remaining tumour tissue (r=0.40) or CSC-II (r=0.26) (P=0.55, 0.23 and 0.49, respectively).

The results of this small retrospective study suggest that CSCs are commonly present in HCC tissue invading the hepatic microvasculature. The results also indicate the percent and distribution of CSCs within the tumour tissue does not predict TTR. Unfortunately, in the absence of samples in which the invading tissue did not contain CSCs and cases in which recurrences did not occur, it was not possible to determine whether the presence or distribution of CSCs are responsible for tumour recurrence. A larger, preferably prospective study is required to address this important question.

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3. Minuk GY, Bautista W, Klein J. Evidence of hepatitis B virus infection in cancer stem cells associated with human hepatocellular carcinoma. Can J Infect Dis Med Microbiol (In press).

TABLE 1
Prevalence and distribution of cancer stem cells (CSC) in hepatocellular carcinoma (HCC) with microvascular invasion

Patient	Age, years	Sex	CLD	# HCC	Size, cm	AFP, µg/L	Follow-up, months	TTR, months	CSC, %		
									Invading edge	Residual	CSC-II
1	67	Male	HBV	1	5.6	27	55.7	48.4	70	54	1.30
2	73	Male	NASH	3	5.4	479	35	28.3	55	55	1.31
3	74	Male	HBV	1	9.5	785	26.9	16.5	39	39	0.56
4	58	Female	NASH	4	13	26	50.7	11.7	79	57	1.39
5	48	Female	HCV	1	5.1	9663	32.8	9.7	93	75	1.24
6	54	Male	HBV	1	8.0	–	101	46.1	69	79	0.87
7	67	Male	NASH	2	2.8	8	29.7	18.2	57	39	1.46
8	73	Female	?	1	10	45	4.8	3.5	48	26	1.85
9	58	Male	NASH	≥4	5	4	10.4	9.1	29	31	0.94
Mean	64	6 Male		1.5±1	7.5±3.0	36	38.5±26.8	21.3±15.4	59.9±18.9	52.6±18.2	1.21±0.36

AFP Alpha fetoprotein; CLD Chronic liver disease; CSC-II CSC invasion index (see text for calculation); HBV Hepatitis B virus; HCV Hepatitis C virus; NASH Nonalcoholic steatohepatitis; TTR Time to recurrence

