Letter to the Editor

Does delayed treatment affect the survival of patients with hepatocellular carcinoma?

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Hepatocellular carcinoma (HCC) progresses at highly variable rates. It is widely believed that active treatment should begin as soon as possible after diagnosis. This may not always occur for various reasons, and it remains unclear whether such delays shorten overall survival.

In a recent issue of the *Journal of Hepatology*, Lim and coworkers (1) addressed this question for patients diagnosed with single HCC at very early or early stages. Their prospective analysis of 100 patients during follow-up extending 33 months from diagnosis showed that patients who underwent resection ≥3 months after diagnosis had similar oncological and long-term outcomes as patients who underwent resection <3 months after diagnosis. While we applaud the authors for tackling this important question, we wish to highlight the need for caution when interpreting their data and drawing conclusions for clinical practice.

One potential issue is the generalizability of their findings. Their patients showed median tumor size of 3.4 (range, 2.2–5.7) cm at diagnosis and 3.5 (range, 2.5–6.2) cm at resection. Thus, few patients had large HCC (>5 cm) or huge HCC (≥10 cm), and tumors had grown by only ~0.1 cm in the interval from diagnosis to surgery. In addition, the difference in median delay until surgery between the "≥3 months" and "<3 months" patient groups was only 2.8 months (4.6 *vs.* 1.8 months). This reflects the fact that 29 of 50 patients (58%) in the "≥3 months" group experienced delays of 3–5 months. These issues raise concern about whether the results of Lim *et al.* can be extrapolated to other patient populations. Another question is whether the apparent lack of effect of delayed surgery extends to the long term, since 15 of 50 patients (30%) in the "≥3 months" group were enrolled after 2015, making follow-up too short to calculate long-term survival.

Our own analysis of literature indexed in PubMed identified several studies involving patients with HCC diagnosed at various stages that come to the opposite conclusion as Lim *et al.* (*Table 1*). Those studies conclude that patients initiating treatment >3 months after diagnosis (4,5), 2 months after diagnosis (3), or even 5 weeks after diagnosis (2) have significantly lower overall and disease-free survival (2) than patients starting treatment earlier.

Just as with other cancers (6), delayed treatment is likely to influence outcomes for patients with HCC. Since life expectancy for many HCC patients without any positive treatment is shorter than 12 months, delaying treatment for more than 3 months often allows substantial tumor growth (7), which is a mortality risk factor in single HCC (8) and is associated with greater incidence of microvascular invasion. In one study, for example, 25% of patients with tumors <2 cm had microvascular invasion, compared to 31% of patients with tumors >2–4 cm and 50% of patients with tumors >4 cm (9).

The question addressed by Lim *et al.* is timely: nearly 30% of HCC patients in Europe and the USA initiate treatment more than 3 months after diagnosis (4). These delays can allow tumor growth and increase risk of

Table 1 Studies indexed in PubMed on the effects of delayed treatment on survival of HCC patients

Study	Inclusion period	n	Tumor stage	Tumor size at diagnosis (cm)	Treatment	Cut-off in treatment delay used to compare patient groups	Median follow-up, months	P value	
								Overall survival	Disease-free survival
Lim 2017 (1)	2006–2016	100	BCLC 0/A	3.4 (2.2–5.7)	Resection	>3 months	29 [16–45]	0.20	0.42
Chen 2011 (2)	2004–2007	121	BCLC A	2.8 (1.3–5.0)	RFA	>5 weeks	25 [8–55]	0.019	0.01
Huo 2007 (3)	1998–2003	144	BCLC A/B	NR	TACE, PAI, PEI	>2 months	28 [3–61]	0.009	NR
Singal 2013 (4)	2005–2012	165	BCLC A/B/C	NR	Resection, LT, RFA, TACE, systemic therapy	>3 months	NR	<0.05	NR
Croome 2010 (5)	2002–2008	350*	NR	NR	NR	>3 months	NR	0.042	NR

The PubMed database was searched in December 2017 with the search terms "delayed treatment" and "hepatocellular carcinoma". Unless otherwise noted, values are reported in the table as n or mean (range). *, only 83 (23.7%) had HCC; BCLC, Barcelona Clinic Liver Cancer; NR, not reported; PAI, percutaneous acetic acid injection; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; LT, liver transplantation.

microvascular invasion, reducing overall survival. Timely delivery of treatment to HCC patients should be improved, especially for those with disease in intermediate or advanced stages (10).

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Footnote

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Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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