Clinical Radiology 74 (2019) 814.e1–814.e7

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Tumour stiffness associated with tumour response to conventional transarterial chemoembolisation for hepatocellular carcinoma: preliminary findings

R. Chen [a,b], W. Kong [c], Y. Gan [a,b], N. Ge [a,b], Y. Chen [a,b], H. Ding [c], J. Luo [d], W. Wang [c], Z. Ren [a,b,*]

[a] Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China
[b] Key Laboratory of Carcinogenesis and Cancer Invasion, Ministry of Education, 136 Yi Xue Yuan Road, Shanghai 200032, China
[c] Department of Ultrasound, Zhongshan Hospital, Fudan University, Shanghai, China
[d] Department of Health Statistics and Social Medicine, School of Public Health, Fudan University, Shanghai, China

ARTICLE INFORMATION

Article history:
Received 30 October 2018
Accepted 16 July 2019

AIM: To evaluate whether elastic (stiffness) characteristics of tumours were associated with treatment responses and survival of patients with hepatocellular carcinoma (HCC) treated with transarterial chemoembolisation (TACE).

MATERIALS AND METHODS: A retrospective cohort study of 59 HCC patients with unresectable HCC who underwent TACE was undertaken. Acoustic radiation force impulse imaging (ARFI) was used to measure tissue stiffness of the index tumours and non-tumoural liver before TACE treatment. The correlation between the parameters of tumour stiffness and treatment response to TACE was assessed using mRECIST criteria as well as according to patient survival.

RESULTS: Tumour stiffness and its stiffness difference between tumour and non-tumoural liver were significantly associated with tumour response to TACE (p=0.019 and 0.010, respectively). Patients with tumour stiffness of <2 m/s or stiffness difference between tumour and non-tumoural liver of <0.5 were more likely to have treatment response to TACE. Univariate analysis showed that the difference in stiffness between tumour and non-tumoural livers (p=0.039) was one of the significant predictors of overall survival (OS). In multivariate analysis, alpha-fetoprotein (AFP) (p=0.006) and Barcelona Clinic Liver Cancer (BCLC) stage (p=0.017) were identified as independent predictors of survival.

CONCLUSION: Tumour stiffness characteristics might be an added predictive marker of treatment response to TACE in patients with HCC.

* Guarantor and correspondent: Z. Ren, Key Laboratory of Carcinogenesis and Cancer Invasion, Ministry of Education, 136 Yi Xue Yuan Road, Shanghai 200032, China.
E-mail addresses: ren.zhenggang@zs-hospital.sh.cn, renzhenggang99@126.com (Z. Ren).

https://doi.org/10.1016/j.crad.2019.07.008
0009-9260/

Introduction

Conventional transarterial chemoembolisation (TACE) is a well-established treatment for unresectable hepatocellular carcinoma (HCC).[1] Randomised clinical trials have showed that TACE improves the survival of patients with unresectable HCC[2,3]; however, some patients cannot achieve similar benefit from TACE.

Early prediction of tumour response is paramount for identification of treatment failure as well as for guidance of future therapy, e.g. repeating or stopping TACE or receiving combined treatment.[4] In actual clinical practices, reduced tumour enhancement on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) at 1–3 months after TACE typically indicates tumour response to treatment. Intra-procedural C-arm CT performed during TACE has recently emerged for prediction of early tumour response.[5] Clinical information, pretreatment imaging characteristics of HCC, or dynamic changes of alpha-fetoprotein (AFP) have also been reported as predictive markers for tumour response to TACE[6,7]; however, there is no widely accepted and reliable method for predicting early therapeutic response to TACE.

Acoustic radiation force impulse imaging (ARFI) is a novel, non-invasive method used to assess tissue stiffness indicated by quantitative measurement of propagating mechanical shear waves in biological tissues.[8] Increased liver stiffness has been associated with HCC incidence, liver-related events, complications after hepatectomy, and tumour recurrence after treatment.[9–12] Moreover, evaluating the stiffness characteristics of focal liver lesions can help differentiate between benign and malignant liver lesions.[13,14] Magnetic resonance elastography (MRE) has recently been used to measure liver tumour stiffness. According to basic research, increased matrix stiffness promotes cell proliferation, chemotherapeutic resistance, and tumour progression of HCC.[15–17] Because tumour stiffness can be used to differentiate benign and malignant liver lesions, whether this biophysical property of tumours could predict treatment response to chemoembolisation has not yet been fully elucidated.

Therefore, this study aimed to assess whether tumour stiffness characteristics were associated with tumour responses to TACE and patient survival after treatment.

Materials and methods

Patients

This retrospective study was approved by the Institutional Review Board. Because of its retrospective nature, the need for patients' informed consent was waived. The inclusion criteria comprised (1) patient with a HCC diagnosis via liver biopsy or typical radiologic appearance; (2) treatment-naive patients who underwent TACE as a first-line therapy between June 2014 and May 2015; (3) preserved liver function with Child–Pugh grade A or B7; (4) performance status of 0–2; (5) patients who underwent ARFI examinations before TACE treatment. The exclusion criteria were (1) diffuse- or infiltrative-type HCC with poorly demarcated borders; (2) distance between the lesion and skin of >8 cm; and (3) lesions obscured by bowel gas or obesity. When measuring ARFI, the patient was instructed to hold their breath for a moment. ARFI acquisitions failed in two patients due to obesity and difficulty in breath holding. Based on these criteria, the final study population included 59 patients. From a prospectively maintained HCC database, variables related to patient demographics; clinical, laboratory, and tumour characteristics; and survival data of each patient were retrieved.

ARFI assessment

One radiologist (with 8 years of experience) performed all ultrasound examinations and was blinded to the information on patient selection and clinical treatment. ARFI was performed in the index lesion targeted for TACE treatment. The tumours were located within an 8-cm distance from the transducer. Siemens Acuson S2000 ultrasound device equipped with ARFI imaging and a 1–4 MHz curved array transducer (4 C1) was used. After performing a conventional greyscale ultrasound to show the target lesion, virtual touch tissue quantification (VTQ) was performed to obtain the quantitative stiffness involving the selection of regions to measure elastic properties using a selected region of interest (ROI) by placing a "measuring box" set at 10×6 mm within the lesion (Fig 1). In regard to the larger tumours (>3 cm in diameter), the ROI analysis for stiffness measurements was conducted on the peripheral tumour region to prevent the potential impact of necrosis. VTQ measures the shear-wave velocity (SWV, expressed in metres per second) in the ROI of lesions and non-tumoural livers at least four times each. ROI of non-tumoural liver was placed at least 2 cm from the focal lesion and at the similar depth as in the previous ROI of the focal lesion to the transducer, excluding

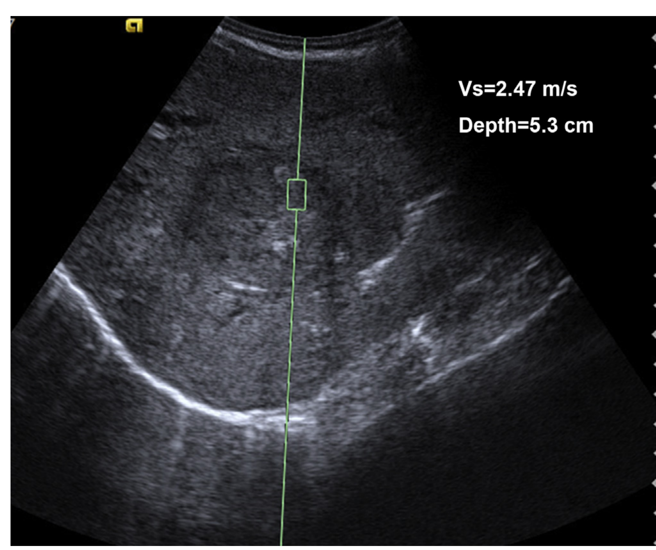

Figure 1 Measurements of acoustic radiation force impulse imaging (ARFI) for a tumour.

any vessels or biliary structures. If invalid readings of SWV values (X.XXX) appeared due to poor ROI positioning or patient movement, measurements were repeated until the required numbers of valid values were obtained. The stiffer the tissue, the faster the shear waves propagate. Data are expressed as the means of four SWV values.

TACE procedure

As previously described, TACE procedures were performed according to institutional protocol.[18,19]

Treatment response

Patients were followed at the outpatient clinic. The treatment response was evaluated by a dynamic contrast-enhanced CT or MRI at 1–3 months after the initial treatment. Response was assessed using modified Response Evaluation Criteria in Solid Tumours (mRECIST) criteria by measuring the longest enhancing dimension on the arterial phase axial images and graded as complete response (CR) of no arterial enhancement in the treated tumour, partial response (PR) of 30% size reduction of the viable lesion, progressive disease (PD) of 20% size increase of the viable lesion, and stable disease (SD) if neither PR or PD criteria were met. Responder means CR or PR, and non-responder includes SD or PD.

Statistical analysis

All data analyses were performed using SPSS 19.0 (IBM, Armonk, NY, USA). The Fisher exact test was used to assess the potential association between clinicopathological variables and treatment response. Receiver operator curve analysis was performed to evaluate the association between clinicopathological characteristics and treatment response using a treatment–response model by comparing responders with non-responders. OS was defined as the interval of time from the date of first TACE to the date of death from any cause, last follow-up evaluation, or data censoring (31 March 2017). Kaplan–Meier analysis was used to generate survival curves that were compared using the log-rank test. Cox proportional hazard regression model was conducted to identify any independent predictors. A $p<0.05$ was considered statistically significant.

Results

Patient demographics

Among the 59 patients included in the present study (Table 1), 50 were men and nine were women, with the median age of 58 (interquartile range [IQR], 50–61) years. Forty-four (44/59, 74.6%) of them were positive for hepatitis B virus surface antigen and two (2/59, 3.4%) were positive for hepatitis C virus antibody. Serum AFP values were normal in 15 patients and >400 ng/ml in 30. Solitary lesions were found in 33 patients, two or three in 15 patients, and four or more in 11 patients. In the case of multiple tumours, the largest tumour targeted during treatment was considered the index lesion. Median tumour size was 7 (IQR, 4–10) cm. Thirteen patients had first- or second-order branch portal vein tumour thrombus (PVTT). In real-world clinical practice, TACE is often conducted to treat HCC patients with PVTT in the Asia–Pacific region, albeit it is not recommended in these patients according to the BCLC staging system. Most patients had good liver function at the time of treatment, with 54 patients having Child–Pugh A and five having Child–Pugh B. Tumour stages were BCLC stage A in 10 patients, stage B in 36, and stage C in 13.

The follow-up period ranged 2–33 months, with a median of 7 months. The mean OS time was 23.6 months (95% confidence interval [CI]: 19.6–27.7 months). Fourteen patients died during the study period, which consisted of 12 patients who died of cancer and two who died of hepatic failure. In total, 124 TACE sessions (median, two sessions; IQR, 1–3 sessions per patient) were performed. The most common complication was post-embolisation syndrome after TACE. No major complications were encountered.

Table 1
Baseline characteristics of the patients.

Variables	All patients (n=59)
Age (years)[a]	58 (50–61)
Gender (male/female)	50/9
BCLC (positive/negative)	44/15
HCV antibody (positive/negative)	2/57
Albumin (g/l)[a]	39 (34–40)
Bilirubin (μmol/l)[a]	12.8 (9.3–18.2)
GGT (IU/l)[a]	122 (56.0–201.0)
ALT (IU/l)[a]	45 (31–67)
AST (IU/l)[a]	59 (44–95)
Platelet ($\times10^9$/l)	150 (75–154)
Prothrombin time (s)[a]	13.0 (12.3–13.6)
AFP (ng/ml)[a]	416.0 (18.1–2675.0)
Child–Pugh grade (A/B)	54/5
Tumour size, diameter of largest tumour (cm)[a]	7.0 (4.0–10.0)
Tumour number (1/2/3/≥4)	33/9/6/11
TACE sessions[a]	2 (1–3)
BCLC stage (A/B/C)	10/36/13

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, alpha-fetoprotein; TACE, transarterial chemoembolisation; BCLC, Barcelona Clinic Liver Cancer; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase.
[a] Values are medians, with interquartile ranges shown in parentheses.

Association between tumour stiffness characteristics and tumour response

According to the mRECIST criteria, four patients had CR, 31 had PR, 20 patients had SD, and four patients had PD after TACE treatment. For the 59 index lesions evaluated by ARFI, HCC stiffness was significantly higher than that of the corresponding non-tumoural liver (mean value, 2.47±0.88 versus 1.88±0.55 m/s, $p<0.001$; Fig 2). A significant association was observed between tumour stiffness and tumour response (CR and PR) to TACE (p=0.019, area under receiver operator curve, AUROC, 0.682; 95% CI: 0.543–0.820; Fig 3), with higher tumour response rates among patients who had tumour stiffness value of <2 m/s (p=0.014, Table 2);

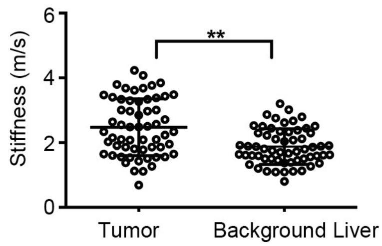

Figure 2 Stiffness of tumour and background liver.

Table 2
Tumour stiffness or stiffness difference between tumour and background liver was associated with tumour response.

Variable	Tumour response	Non-tumour response	*p*-Value
Tumour stiffness (m/s)			
≤2	17	4	0.014
>2	18	20	
Stiffness difference between tumour and background liver			
≤0.5	25	8	0.007
>0.5	10	16	

however, there was no significant correlation between the stiffness of non-tumoural livers and treatment response (p=0.371). Remarkably, the stiffness difference between tumour and non-tumoural livers was statistically significantly associated with tumour response (p=0.010, AUROC, 0.699; 95% CI: 0.560–0.839; Fig 3). Patients with the stiffness difference between tumour and non-tumoural liver of <0.5 were more likely to have positive treatment response to TACE (p=0.007, Table 2). In addition, in patients with a low-degree cirrhosis (using the median stiffness of non-tumoural livers as the cut-off value), the stiffness difference between tumour and non-tumoural livers was statistically significantly associated with tumour response (p=0.024, AUROC, 0.742; 95% CI: 0.548–0.936); however, the stiffness difference between tumour and non-tumoural livers was not significantly associated with tumour response (p=0.383, AUROC, 0.603; 95% CI: 0.388–0.818) in patients with high-degree cirrhosis. This suggests that the difference between tumour and non-tumoural livers can predict tumour response in patients with low-degree cirrhosis.

Tumour size was also a statistically significantly associated with tumour treatment response (p=0.005, AUROC, 0.718; 95% CI: 0.584–0.852; Fig 2). Mean tumour size among patients who responded to TACE was 6.2±3.5 cm, which was significantly smaller than those with mean tumour size of 9±3.7 cm among the patients who did not respond to TACE.

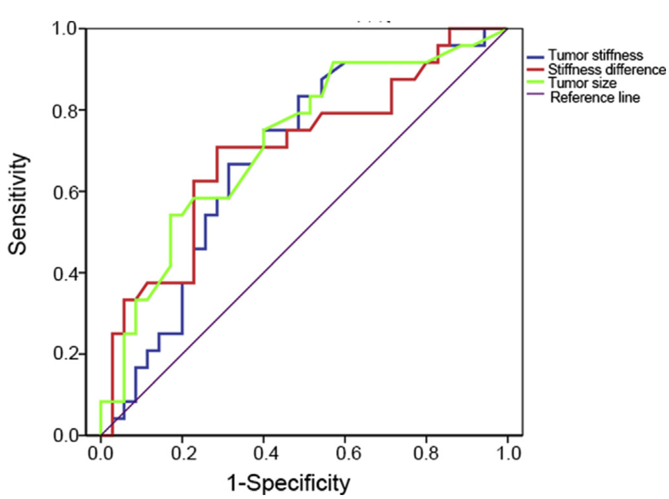

Figure 3 ROC analysis of tumour stiffness, stiffness between tumour and background liver, and tumour size to discriminate between tumour response (CR + PR) and a non-tumour response (SD + PD) to TACE.

Tumour size was also not significantly correlated with tumour stiffness (r=0.205, p=0.120) and with stiffness difference between tumour and background livers (r=0.201, p=0.127).

Association between tumour stiffness characteristics and survival

Using univariate analyses, alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), tumour size, BCLC stage, stiffness difference between tumour and non-tumoural liver (p=0.039) were significant predictors of OS; however, tumour stiffness was not associated with OS (p=0.52; Table 3). In the multivariate analysis, neither tumour stiffness nor stiffness difference between tumour and non-tumoural livers was associated with patient OS, whereas AFP (p=0.006) and BCLC stage (p=0.017) were identified as independent predictors of OS.

Discussion

Early prediction of tumour response is an important guide for future therapy in order to facilitate communication between physicians and their patients. In addition, it will help select patients who are appropriate for the TACE treatment. In this study, tumour stiffness value was identified as an additional predictive marker for treatment response to TACE in patients with HCC. Tumour stiffness might also be used as a marker for early treatment response to TACE. Therefore, tumour stiffness characteristics as additional pretreatment information might be useful in selecting patients with HCC who are suitable for TACE. The present findings might have clinical implications in improving the outcome of TACE.

TACE is the mainstay treatment for patients with unresectable HCC[20]; however, the prognosis of patients treated by TACE greatly varies due to the patient and tumour heterogeneity.[21,22] In particular, tumour heterogeneity is an important biomarker for tumour response to treatment, such as genomic inhomogeneity, cellularity, angiogenesis, and extracellular matrix at a microscopic level.[6,23,24] The number of studies quantifying tumour heterogeneity and its association with treatment responses has been increasing.[6,23] Aside from traditional criteria (e.g., tumour

Table 3
Univariate and multivariate analyses of variables associated with survival of the patients after TACE.

Variable	Univariate		Multivariate	
	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Age	0.972 (0.918–1.030)	0.343		
Gender	0.598 (0.165–2.169)	0.434		
HBsAg	0.604 (0.135–2.707)	0.510		
Albumin	1.400 (0.445–4.400)	0.565		
Bilirubin	1.023 (0.964–1.086)	0.450		
GGT	1.003 (1.000–1.006)	0.057		
ALT	1.010 (1.001–1.020)	0.039		
AST	1.011 (1.002–1.020)	0.018		
Platelet	1.003 (0.998–1.009)	0.205		
Prothrombin time	0.993 (0.658–1.499)	0.974		
AFP	1.000 (1.000–1.000)	<0.001	1.000 (1.000–1.000)	0.006
Tumour size	1.253 (1.074–1.463)	0.004		
Tumour number	0.983 (0.650–1.487)	0.935		
Tumour stiffness	1.605 (0.909–2.832)	0.103		
Stiffness of non-tumoural liver	0.729 (0.277–1.924)	0.524		
Stiffness difference between tumour and non-tumoural liver	1.936 (1.034–3.625)	0.039		
BCLC stage		0.003		0.017
A versus C	0.040 (0.004–0.376)	0.005	0.066 (0.006–0.671)	0.022
B versus C	0.175 (0.053–0.574)	0.004	0.204 (0.059–0.709)	0.012

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, alpha-fetoprotein; TACE, transarterial chemoembolisation; BCLC, Barcelona Clinic Liver Cancer; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase.

size), pre-therapy imaging characteristics, such as tumour vascularity, perfusion, and contrast-enhanced texture analysis, have been reported as early imaging markers for treatment response.[23,25,26] Previous studies have suggested that tumour enhancement on CT is associated with treatment response after chemoembolisation. With the use of quantifying tumour blood flow features, Reis *et al.*[6] reported that tumour heterogeneity and arterial phase enhancement were predictive markers for treatment response to drug-eluting bead chemoembolisation in patients with HCC. Different from these studies, the present study showed that tumour stiffness characteristics and biophysical tumour properties could be considered as a predictive marker for treatment response in patients with HCC treated by TACE.

Liver stiffness has been associated with HCC incidence, liver-related events, or tumour recurrence after treatment.[27–29] In contrast, tumour stiffness evaluated by ARFI is useful not only to distinguish benign and malignant liver lesions,[30] but also help detect recurrent HCC after radiofrequency ablation treatment.[10,12] Moreover, in a recent study, Gordic *et al.*[31] reported that tumour stiffness measured with MRE was correlated tumour enhancement and necrosis in HCC patients treated with locoregional therapies. The present study provided additional pretreatment information that tumour stiffness characteristics might predict the treatment response to TACE in patients with HCC, which could help select the distinct subgroup of patients who are suitable for TACE treatment to yield a better survival outcome. Low pretreatment tumour stiffness values of tumours might commonly predict better outcomes. Tumour stiffness characteristic could be used to classify HCC lesions that are responding or not to treatment. Patients with tumour stiffness of <2 m/s or stiffness difference between tumour and non-tumoural liver of <0.5 might more likely result in better treatment response (CR or PR) to TACE. If HCC patients with high tumour stiffness might be less likely to respond to TACE, an alternative therapy such as combined with ablation, radiation, or sorafenib could be planned. Therefore, tumour stiffness characteristic might be a new non-invasive assessment method of tumour response to TACE.

Tumour stiffness (elasticity) is associated with tumour cellularity, tumour grade, vascularity, and necrosis,[31,32] which reflects tumour biology and is of great clinical importance. Ling *et al.*[33] found that higher tumour stiffness was observed in hypervascular and poorly differentiated HCC than that in hypovascular and moderately to well-differentiated lesions. On the contrary, one report demonstrated that tumour stiffness appeared to be higher in moderate/well differentiated HCC.[32] Esser *et al.*[34] showed that the higher the tumour stiffness in HCC, the larger the tumour. Higher tumour stiffness before treatment is significantly associated with tumour recurrence after the locoregional treatment or surgical resection.[35,36] This may explain the present findings that tumour stiffness could influence treatment response to TACE. Furthermore, reduced tumour stiffness after treatment has been reportedly correlated with tumour necrosis extent,[31] providing early evidence for a therapeutic response.

In the present study, AFP and BCLC stage were identified as independent factors influencing patient survival in multivariate analyses; however, either tumours stiffness or its stiffness difference between tumour and non-tumoural liver was not associated with patients' OS. This result can be validated in future studies.

This study has several limitations. First, the major limitation is an uncontrolled retrospective analysis in a small number of patients. Measured and unmeasured confounders may be present. Therefore, it is susceptible to various biases, which may compromise the conclusion. The present findings should be further validated and explored. Second, tumour response was evaluated based on an index lesion, not on a patient basis. This could lead to an overestimation of tumour response after TACE. Third, ARFI imaging (point-SWE) was used, involving a single acoustic impulse to induce a shear wave within a small ROI ($\sim 1\times 0.6$ cm). The size of the ROI did not cover the entire tumour; therefore, it may not reflect the heterogeneity of the entire tumour. In other words, tumour heterogeneity (inhomogeneous tissue) leads to different levels of stiffness in various tumour regions, and stiffness measurement in the HCC ROI may not be representative and reproducible of the full extent of stiffness variation within a tumour. These weaknesses limit the power of the study.

In conclusion, the present study suggests that tumour stiffness characteristics quantified by ARFI analysis might be an added predictor of HCC treatment response to TACE.

Conflict of interest

The authors declare no conflict of interest.

References

1. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;**42**:1208–36.
2. Llovet JM, Real MI, Montana X, *et al*. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;**359**:1734–9.
3. Lo CM, Ngan H, Tso WK, *et al*. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;**35**:1164–71.
4. Stroehl YW, Letzen BS, van Breugel JM, *et al*. Intra-arterial therapies for liver cancer: assessing tumour response. *Expert Rev Anticancer Ther* 2017;**17**:119–27.
5. Loffroy R, Lin M, Yenokyan G, *et al*. Intraprocedural C-arm dual-phase cone-beam CT: can it be used to predict short-term response to TACE with drug-eluting beads in patients with hepatocellular carcinoma? *Radiology* 2013;**266**:636–48.
6. Reis SP, Sutphin PD, Singal AG, *et al*. Tumour enhancement and heterogeneity are associated with treatment response to drug-eluting bead chemoembolization for hepatocellular carcinoma. *J Comput Assist Tomogr* 2017;**41**:289–93.
7. Riaz A, Ryu RK, Kulik LM, *et al*. Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival. *J Clin Oncol* 2009;**27**:5734–42.
8. Park H, Park JY, Kim DY, *et al*. Characterization of focal liver masses using acoustic radiation force impulse elastography. *World J Gastroenterol* 2013;**19**:219–26.
9. Vermehren J, Polta A, Zimmermann O, *et al*. Comparison of acoustic radiation force impulse imaging with transient elastography for the detection of complications in patients with cirrhosis. *Liver Int* 2012;**32**:852–8.
10. Xu X, Luo L, Chen J, *et al*. Acoustic radiation force impulse elastography for efficacy evaluation after hepatocellular carcinoma radiofrequency ablation: a comparative study with contrast-enhanced ultrasound. *BioMed Res Int* 2014;**2014**:901642.
11. Kang J, Kwon H, Cho J, *et al*. Comparative study of shear wave velocities using acoustic radiation force impulse technology in hepatocellular carcinoma: the extent of radiofrequency ablation. *Gut Liver* 2012;**6**:362–7.
12. Kwon HJ, Kang MJ, Cho JH, *et al*. Acoustic radiation force impulse elastography for hepatocellular carcinoma-associated radiofrequency ablation. *World J Gastroenterol* 2011;**17**:1874–8.
13. Heide R, Strobel D, Bernatik T, *et al*. Characterization of focal liver lesions (FLL) with acoustic radiation force impulse (ARFI) elastometry. *Ultraschall Med* 2010;**31**:405–9.
14. Rizzo L, Nunnari G, Berretta M, *et al*. Acoustic radial force impulse as an effective tool for a prompt and reliable diagnosis of hepatocellular carcinoma — preliminary data. *Eur Rev Med Pharmacol Sci* 2012;**16**:1596–8.
15. Schrader J, Gordon-Walker TT, Aucott RL, *et al*. Matrix stiffness modulates proliferation, chemotherapeutic response, and dormancy in hepatocellular carcinoma cells. *Hepatology* 2011;**53**:1192–205.
16. You Y, Zheng Q, Dong Y, *et al*. Matrix stiffness-mediated effects on stemness characteristics occurring in HCC cells. *Oncotarget* 2016;**7**:32221–31.
17. Wells RG. The role of matrix stiffness in regulating cell behavior. *Hepatology* 2008;**47**:1394–400.
18. Yin X, Zhang L, Wang YH, *et al*. Transcatheter arterial chemoembolization combined with radiofrequency ablation delays tumor progression and prolongs overall survival in patients with intermediate (BCLC B) hepatocellular carcinoma. *BMC Cancer* 2014;**14**:849.
19. Zhang L, Yin X, Gan YH, *et al*. Radiofrequency ablation following first-line transarterial chemoembolization for patients with unresectable hepatocellular carcinoma beyond the Milan criteria. *BMC Gastroenterol* 2014;**14**:11.
20. Lencioni R, de Baere T, Soulen MC, *et al*. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. *Hepatology* 2016;**64**(1):106–16.
21. Bolondi L, Burroughs A, Dufour JF, *et al*. Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis* 2012;**32**:348–59.
22. Hsu CY, Liu PH, Hsia CY, *et al*. Nomogram of the Barcelona Clinic Liver Cancer system for individual prognostic prediction in hepatocellular carcinoma. *Liver Int* 2016;**36**(10):1498–506.
23. Reiner CS, Gordic S, Puippe G, *et al*. Histogram analysis of CT perfusion of hepatocellular carcinoma for predicting response to transarterial radioembolization: value of tumour heterogeneity assessment. *Cardiovasc Intervent Radiol* 2016;**39**:400–8.
24. Lu LC, Hsu CH, Hsu C, *et al*. Tumour heterogeneity in hepatocellular carcinoma: facing the challenges. *Liver Cancer* 2016;**5**:128–38.
25. Zhao JG, Feng GS, Kong XQ, *et al*. Assessment of hepatocellular carcinoma vascularity before and after transcatheter arterial chemoembolization by using first pass perfusion weighted MR imaging. *World J Gastroenterol* 2004;**10**:1152–6.
26. Kloth C, Thaiss WM, Kargel R, *et al*. Evaluation of texture analysis parameter for response prediction in patients with hepatocellular carcinoma undergoing drug-eluting bead transarterial chemoembolization (DEB-TACE) using biphasic contrast-enhanced CT image data: correlation with liver perfusion CT. *Acad Radiol* 2017;**24**(11):1352–63.
27. Li ZQ, Hu CL, Yu P, *et al*. The development of hepatocarcinoma after long-term antivirus treatment of Chinese patients with chronic hepatitis B virus infection: incidence, long-term outcomes and predictive factors. *Clin Res Hepatol Gastroenterol* 2017;**41**:311–8.
28. Lee HW, Yoo EJ, Kim BK, *et al*. Prediction of development of liver-related events by transient elastography in hepatitis B patients with complete virological response on antiviral therapy. *Am J Gastroenterol* 2014;**109**:1241–9.
29. Lee YR, Park SY, Kim SU, *et al*. Using transient elastography to predict hepatocellular carcinoma recurrence after radiofrequency ablation. *J Gastroenterol Hepatol* 2017;**32**:1079–86.
30. Zhang P, Zhou P, Tian SM, *et al*. Application of acoustic radiation force impulse imaging for the evaluation of focal liver lesion elasticity. *Hepatobiliary Pancreat Dis Int* 2013;**12**:165–70.
31. Gordic S, Ayache JB, Kennedy P, *et al*. Value of tumour stiffness measured with MR elastography for assessment of response of hepatocellular carcinoma to locoregional therapy. *Abdom Radiol (NY)* 2017;**42**:1685–94.
32. Thompson SM, Wang J, Chandan VS, *et al*. MR elastography of hepatocellular carcinoma: correlation of tumour stiffness with histopathology features—preliminary findings. *Magn Reson Imaging* 2017;**37**:41–5.

33. Ling W, Lu Q, Lu C, *et al*. Effects of vascularity and differentiation of hepatocellular carcinoma on tumour and liver stiffness: *in vivo* and *in vitro* studies. *Ultrasound Med Biol* 2014;**40**:739–46.
34. Esser M, Schneeweiss S, Kolb M, *et al*. Comparison between acoustic radiation force impulse quantification data and perfusion-CT parameters in hepatocellular carcinoma. *Eur J Radiol* 2017;**89**:215–20.
35. Praktiknjo M, Krabbe V, Pohlmann A, *et al*. Evolution of nodule stiffness might predict response to local ablative therapy: a series of patients with hepatocellular carcinoma. *PloS One* 2018;**13**:e0192897.
36. Wang J, Shan Q, Liu Y, *et al*. 3D MR elastography of hepatocellular carcinomas as a potential biomarker for predicting tumour recurrence. *J Magn Reson Imaging* 2019 Mar;**49**(3):719–30.