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ULTRASOUND

Evaluation of liver parenchyma stiffness in patients with liver tumours: optimal strategy for shear wave elastography

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Abstract

Objectives To determine the methodology of non-invasive test for evaluation of liver stiffness (LS) with tumours using two-dimensional (2D) shear wave elastography (SWE).

Methods One hundred and twenty-seven patients with liver tumours underwent 2D-SWE before surgery to measure liver and spleen stiffness (SS). Two-dimensional SWE values were obtained in the liver at 0–1 cm, 1–2 cm and >2 cm from the tumour edge (PLS-1, PLS-2 and RLS, respectively). The influence of tumour-associated factors was evaluated. The area under the receiver operating characteristic curve (AUC) for each value was analysed to diagnose cirrhosis.

Results PLS-1 was higher than PLS-2, which was even higher than RLS ($p < 0.001$). The AUCs of PLS-1, PLS-2, RLS and SS for diagnosing cirrhosis were 0.760, 0.833, 0.940 and 0.676, with the specificity of 75.7%, 67.6%, 90.3% and 77.4%, respectively. Tumour sizes, locations or types showed no apparent influence on 2D-SWE values except for RLS, which was higher in patients with primary hepatic carcinomas ($p < 0.05$).

Conclusions LS with tumours is best measured at >2 cm away from the tumour edge. SS measurement could be used as an alternative to LS measurement in the event of no available liver for detection.

Key Points

- *Tumour-associated factors impact background liver stiffness assessment.*
- *Background liver stiffness is best measured at >2 cm from tumour edge.*
- *Spleen stiffness can be an alternative to assess background liver stiffness.*

Keywords Elasticity imaging techniques · Ultrasonography · Liver neoplasms · Liver cirrhosis · Spleen

Abbreviations

2D-SWE	Two-dimensional shear wave elastography
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Glutamate pyruvate transaminase
AST	Glutamic oxaloacetic transaminase

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CCC	Cholangiocellular carcinoma
CV	Coefficient of variation
DBIL	Direct bilirubin
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology
GGT	Glutamyl transpeptidase
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
LS	Liver stiffness
MHC	Metastatic hepatic carcinoma
PHLF	Post-hepatectomy liver failure
PLS	Peritumoural liver stiffness,
PLS-1	Peritumoural liver stiffness measured at 0–1 cm from the tumour edge
PLS-2	Peritumoural liver stiffness measured at 1–2 cm from the tumour edge
PT	Prothrombin time
RLS	Remnant liver stiffness
SS	Spleen stiffness
SSI	Supersonic shear imaging
TBIL	Total bilirubin
TE	Transient elastography

Introduction

Surgical resection is the first treatment choice for patients with primary or secondary liver tumours [1]. Extensively using major hepatectomy increases the risk of post-hepatectomy liver failure (PHLF), post-resection mortality and length of hospital stay [2, 3]. PHLF occurrence reaches 20% in patients with chronic liver disease or cirrhosis [4, 5], which is four times that in those with normal livers. The cirrhotic liver has a poor tolerance for acute tissue loss, given its impaired function and decreased regenerative ability [6]. Preoperative assessment including evaluation of liver stiffness of the future remnant liver is essential prior to hepatectomy [7].

Ultrasound-based elastographic methods for non-invasively measuring liver stiffness (LS) have been widely used as replacements for liver biopsy, which is limited by its invasiveness, sampling error and inter- and intra-observer variabilities during microscopic evaluation [8–10]. Shear wave elastography (SWE) displays shear wave speed calculated using time-varying displacement data to measure the arrival time of a shear wave at various locations [11, 12]. Transient elastography (TE) performed in a one-dimensional ultrasound system has been well studied and recommended for non-invasively staging hepatic fibrosis [13, 14], despite certain limitations [15]. However, two-dimensional (2D) SWE using supersonic shear imaging (SSI) allows real-time visualisation of obtained measurements, guided by anatomy and tissue stiffness. This approach has a lower failure rate and at least similar or better diagnostic performance for fibrosis staging than TE [16–19]. It has been recommended with broad consensus by the 2017 European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines and Recommendations on the clinical use of elastography as the first-line assessment for liver fibrosis severity in patients with chronic liver diseases to identify those with cirrhosis [20–22].

Factors influencing 2D-SWE measurements in diffuse liver disease have been well studied [23–25]. However, with increasing applications in liver tumours, such as liver fibrosis assessment [26] and PHLF prediction [27, 28], no specific recommendation has been reported on how to perform a reliable LS measurement considering the potential tumour influence using 2D-SWE. Although spleen stiffness (SS) correlated with liver fibrosis staging in patients with chronic hepatitis B [19] and could be used for detecting portal hypertension [29], its use in assessing LS in patients with liver tumours is still poorly understood.

Thus, this study aimed to determine the methodology of non-invasive test for preoperative evaluation of background LS in patients with liver tumours using 2D-SWE, and to evaluate the influence of tumour-associated factors including size, location, type of mass and relative accuracy of 2D-SWE measurements obtained from different acquisition sites for diagnosing liver cirrhosis.

Materials and methods

Patients and study design

This prospective study was approved by our local institutional review board; written informed consent was obtained from all patients. Between August 2015 and June 2016, all patients with liver tumours were admitted to our department for LS assessment with 2D-SWE prior to scheduled surgical resection. Inclusion criteria were presence of a liver tumour using conventional ultrasound (US), indication for hepatectomy and tumour diameter of >1 cm. Exclusion criteria were history of chemotherapy or local treatment of liver tumours such as transcatheter arterial chemoembolisation and ablation, ascites, serum transaminases levels (>5× ULN), extra-hepatic cholestasis, right heart failure [14] , body mass indexes (BMI) greater than 30 kg/m^2, inability of patients to control respiration and failure of 2D-SWE measurement [12]. Totally, 160 patients were considered for inclusion and 15 were excluded. Baseline US was performed followed by 2D-SWE measurements in the liver and spleen in 145 patients (Fig. 1).

Fibrosis or cirrhosis diagnosis was confirmed by pathology after surgery and scored with the histology-based Scheuer staging system as the diagnostic reference [30]. According to the system, hepatic fibrosis was staged as follows: S0 = no fibrosis, S1 = enlarged portal fibrosis, S2 = periportal fibrosis ± periportal septa, S3 = architectural distortion but no obvious cirrhosis and S4 = cirrhosis (probable or definite).

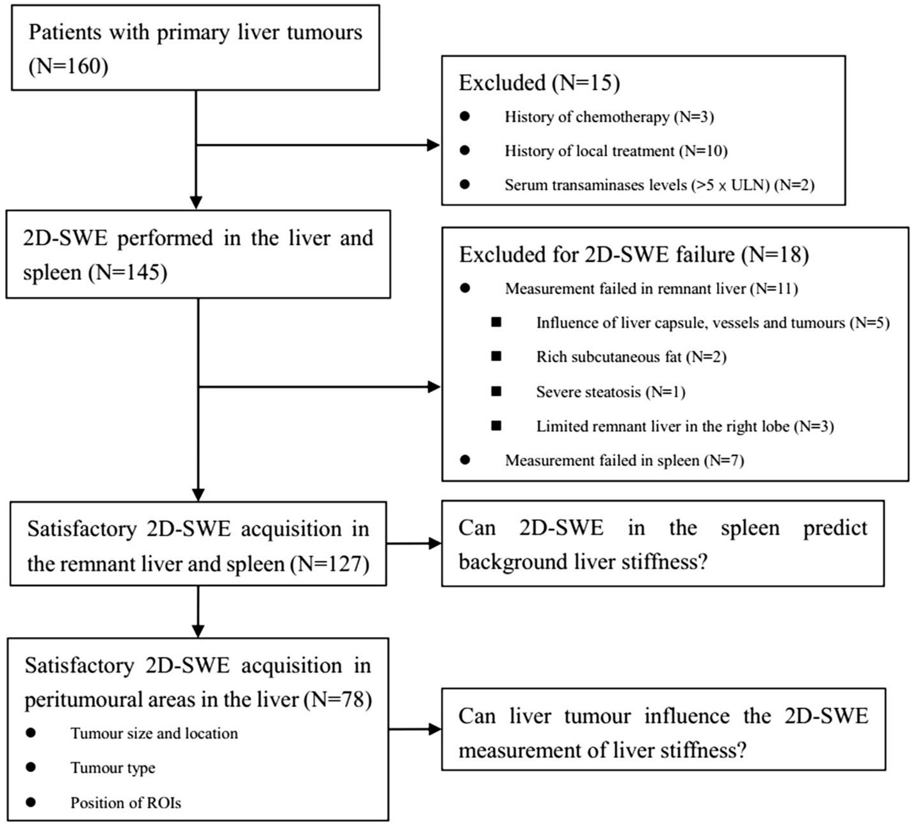

Fig. 1 Schematic of the study population (*2D-SWE* two-dimensional shear wave elastography, *ROI* region of interest)

The following characteristics were recorded: sex, age, tumour size and location, and hepatitis history. Tumour sizes were recorded as maximum diameters and classified into four groups (1–4 cm, 4.1–6 cm, 6.1–10 cm and >10 cm). For patients with multiple lesions, the tumour size was measured as the sum of the maximum diameters of all lesions. Tumour locations were recorded as left lobe, right lobe or both lobes.

Laboratory examinations, including tests for viral markers [hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus, hepatitis D virus, hepatitis E virus)], glutamic oxaloacetic transaminase (AST), glutamate pyruvate transaminase (ALT), alkaline phosphatase (ALP), glutamyl transpeptidase (GGT), albumin, total bilirubin and prothrombin time, were performed within 24 h prior to 2D-SWE measurements. Patients were classified using the Child-Pugh score.

2D-SWE

All 2D-SWE measurements were performed using the Aixplorer US system (Aixplorer; SuperSonic Imagine, Aix-en-Provence, France) with a convex broadband probe (SC6–1) as recommended by one radiologist (W.Z. with 4 weeks of 2D-SWE training and experience with >50 cases and with 10 years of experience in hepatic ultrasonography).

LS measurements were performed through intercostal spaces with patients in the supine position and the right arm maximally abducted. Patients fasted for a minimum of 2 h and rested for a minimum of 10 min before undergoing LS measurements. LS values were obtained in the remnant liver parenchyma (RLS: >2 cm from the tumour edge) and peritumoural liver parenchyma (PLS; PLS-1 and PLS-2: 0–1 cm and 1–2 cm from the tumour edge), respectively. SS measurements were performed in the lateral position with the left arm in maximum extension by placing the probe in left intercostal spaces.

Two-dimensional SWE mode was engaged during a transient breath-hold in the neutral position, avoiding previous deep inspiration [21]. The 2D-SWE image was then displayed as a colour overlay on top of the conventional B-mode image. Two-dimensional SWE measurement was considered valid when the elastography colour map was filled and stable for at least 3 s before acquisition and the region of interest (ROI) was homogenously colour-coded with placement in an isoechoic area of the parenchyma (no large vessel, nodule or other structure), 1–2 cm beneath the liver capsule or 1 cm beneath the spleen capsule [23, 24, 31]. ROI diameters were 10 mm in the peritumoural areas of the liver and 15–20 mm in the remaining liver and spleen. A stiffness value was automatically displayed as the mean of Young's modulus within the ROI by the US system and expressed in kilopascals (kPa) (Fig. 2). A minimum of three different ROIs were measured for each value in the liver and spleen. Each value was recorded; the final stiffness value was calculated as the mean of the recorded acquisitions.

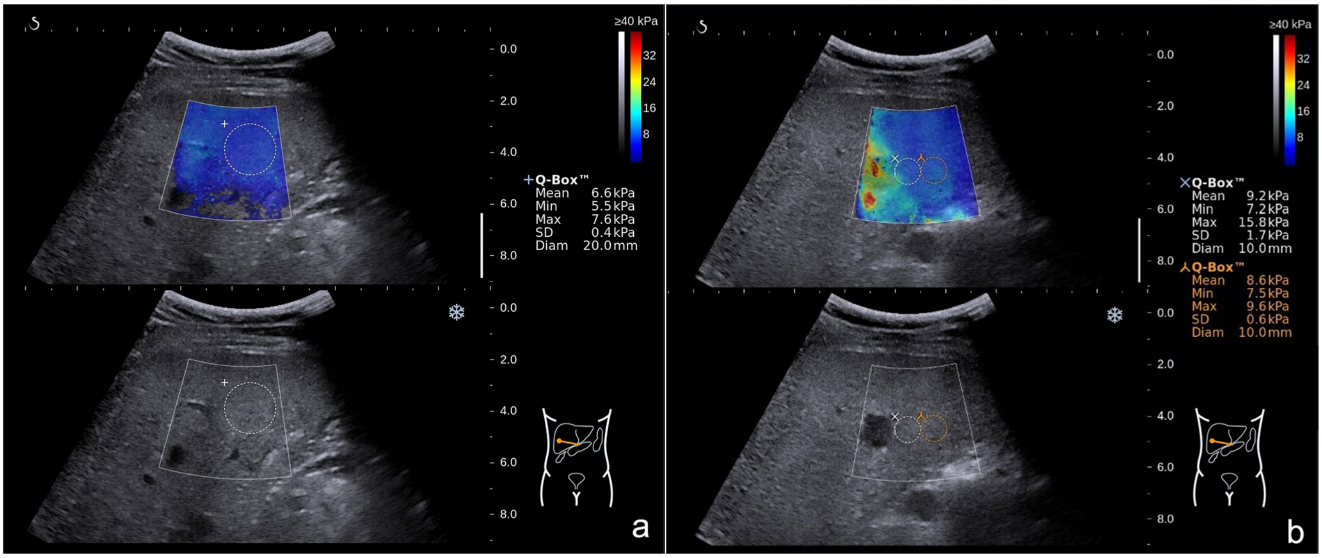

Fig. 2 Elasticity map in the liver obtained with shear wave elastography. Liver stiffness measurements were performed in the remnant liver (**a** >2 cm from the tumour edge) and in peritumoural areas (**b** 0–1cm and 1–2 cm from the tumour edge) with stiffness values displayed as 6.6 kPa, 9.2 kPa, and 8.6 kPa, respectively

Statistical analysis

Quantitative variables of baseline characteristics and 2D-SWE parameters were expressed as median, interquartile range and coefficient of variation (CV). Comparisons between quantitative variables were performed using the Mann-Whitney *U* test, Kruskal-Wallis test or one-way analysis of variance when appropriate. Comparisons between categorical variables were performed using Pearson chi-squared or Fisher's exact test when appropriate. Relationships between parameters were characterised with Pearson's correlation coefficient. The discriminative values of RLS, SS, PLS-1 and -2 for identifying cirrhosis of the remaining liver were assessed by measuring the area under the receiver operating characteristic curve (AUC). Optimal cut-off values maximising the sum of sensitivities and specificities were chosen, and positive and negative predictive values as well as diagnostic accuracy were computed for these cut-off values. AUCs and odds ratios (for logistic regression) were provided with 95% confidence intervals (CIs). Comparison between AUCs was performed using the DeLong method [32]. All tests were two-sided; 0.05 was considered to indicate significance. Data handling and analysis were performed with SPSS software, version 21.0 (IBM, Armonk, New York).

Results

Technical success rate

Two-dimensional SWE measurements were performed in 145 patients. RLS and SS measurements were successful in 134 patients (92.4%) and 138 patients (95.2%). Finally, 127 of 145 patients (87.6%) had applicable RLS and SS measurements, and 78 of 127 patients (61.4%) had applicable PLS measurements (Fig. 1).

The technical success rate of RLS was similar to that of SS (p = 0.999) but higher than that of PLS (p < 0.001). RLS measurements failed in 11 patients because of rich subcutaneous fat (n = 2), severe steatosis (n = 1), limited remnant liver in the right lobe (n = 3) and the influence of liver capsules, vessels and tumours (n = 5), and SS measurement failed in 7 patients because of the small size or poor position of the spleen. PLS measurements were unreliable in 49 patients because of ROI of peritumoura area measured by subcostal approach (n = 21), <1 cm beneath the liver capsule (n = 12), poor B-mode image (n = 12), reverberations (n = 4).

Baseline characteristics (n = 127)

Basic characteristics such as demographic data, blood test and histological results of the 127 patients were summarised in Table 1. No patients were chronically infected with hepatitis C, D and E. According to the Scheuer scoring system, the histopathological results revealed that more than half of the patients (n = 65, 51.2%) were in stage S4, a few patients (n = 4, 3.1%) were in stage S1, 15 (11.8%) patients were in stage S2, and 25 (19.7%) patients were in stage S3 (Table 1).

Study of tumour-related impact factors (n = 78)

Tumour size

No 2D-SWE values were related to the maximum diameters of liver tumours (PLS-1, p = 0.294; PLS-2, p = 0.205; RLS, p

Table 1 Demographic data, blood test and histological results in patients with tumours (n = 127)

Characteristics	All patients (n = 127)
Male	105 (82.7)
Age (years)	53 (19–79)
Hepatitis B	95 (74.8)
Tumour diameter (mm)	52 (34–78)
Tumour location	
Left lobe	37 (29.1)
Right lobe	80 (63)
Both lobes	10 (7.9)
Tumour pathology	
HCC	102 (80.3)
CCC	4 (3.2)
Mixed HCC and CCC	5 (3.9)
MHC	7 (5.5)
Blood tests	
ALT (U/L)	31.2 (23.1–42.1)
AST (U/L)	27.9 (22.6–41.7)
ALP (U/L)	83.2 (68.5–103.0)
GGT (U/L)	47.0 (29.2–84.6)
Child-Pugh score	
Class A	125 (98.4)
Class B	2 (1.6)
Fibrosis score (Scheuer)	
S0	18 (14.2)
S1	4 (3.1)
S2	15 (11.8)
S3	25 (19.7)
S4	65 (51.2)

Unless otherwise indicated, data are presented as numbers of patients, with percentages *in parentheses*, or medians, with interquartile ranges *in parentheses*, except for age, which was expressed as the median, with the range *in parentheses*

HCC hepatocellular carcinoma, *CCC* cholangiocellular carcinoma, *MHC* metastatic hepatic carcinoma, *AST* glutamic oxaloacetic transaminase, *ALT* glutamate pyruvate transaminase, *ALP* alkaline phosphatase, *GGT* glutamyl transpeptidase

= 0.429; SS, p = 0.911). These values did not differ among the four groups of different tumour sizes (PLS-1, p = 0.617; PLS-2, p = 0.558; RLS, p = 0.350; SS, p = 0.862) (Table 2).

Tumour location

No 2D-SWE values differed among three groups of different tumour locations (PLS-1, p = 0.468; PLS-2, p = 0.732; RLS, p = 0.919; SS, p = 0.507) (Table 2).

Tumour type

RLS was higher (p = 0.021) in patients with primary hepatic tumours (HCC, CCC, or mixed HCC and CCC) than in those with other tumours, whereas PLS-1, PLS-2 and SS showed no difference (Table 2).

Position of ROI

PLS-1, PLS-2 and RLS represented LS values obtained at different distances from the tumour. In all groups of different fibrosis stages, tumour sizes or locations, PLS-1 was higher than PLS-2, PLS-2 was higher than RLS (p < 0.05) (Fig. 3, Tables 2 and 3). The coefficient of variation of RLS (CV = 50.5%) was higher than that of PLS-1 and PLS-2 (CV = 33.9% and 34.5%).

Diagnostic performance of elasticity parameters

Overall, 40 of the 127 patients (31.5%) and 25 of the 78 patients (32.1%) were pathologically diagnosed with advanced fibrosis (S2–S3), and 65 of the 127 patients (51.2%) and 41 of the 78 patients (52.6%) were pathologically diagnosed with cirrhosis (S4). RLS linearly correlated to PLS-1, PLS-2 and SS (r = 0.514, p < 0.001; r = 0.673, p < 0.001 and r = 0.519, p < 0.001, respectively). All 2D-SWE values increased with progression of fibrosis stages (p < 0.001 or p = 0.001) (Table 3). RLS could distinguish fibrosis stage S2–S3 from S0–S1 (p = 0.018) and stage S4 from S2–S3 stage (p < 0.001). For PLS-1, PLS-2 and SS, there were overlaps between stage S0–S1 and S2–S3 (p = 0.471, p = 0.160 and p = 0.088, respectively), but they could distinguish stage S4 from S2–S3 (p = 0.001, p < 0.001 and p = 0.018, respectively).

The AUCs of PLS-1, PLS-2, RLS and SS for distinguish advanced fibrosis (stage≥S2) were 0.720 (95% CI = 0.575–0.866, p = 0.016), 0.785 (95% CI = 0.634–0.936, p = 0.002), 0.925 (95% CI = 0.879–0.971, p < 0.001) and 0.703 (95% CI = 0.589–0.817, p = 0.003), with optimal cut-offs of 14.1, 9.1, 8.3 and 20.5 kPa, respectively (Table 4). The ROC curves of PLS-1, PLS-2, RLS and SS drawn to differentiate liver cirrhosis (stage = S4) provided AUCs of 0.760 (95% CI = 0.654–0.865, p < 0.001), 0.833 (95% CI = 0.742–0.924, p < 0.001), 0.940 (95% CI = 0.902–0.977, p < 0.001) and 0.676 (95% CI = 0.584–0.767, p = 0.001), with optimal cut-offs of 15.0, 10.9, 9.9 and 21.4 kPa, respectively (Table 5, Fig. 4). The AUC of RLS was significantly higher than those of PLS-1, PLS-2 and SS, which did not differ from each other.

Discussion

In this prospective study, we evaluated the influence factors and practical issues of non-invasive test for preoperative evaluation of liver parenchyma in patients with liver tumours using 2D-SWE, by following the basic well-defined recommendations from 2017 EFSUMB Guidelines to the fullest extent.

The initial finding of our study was that 2D-SWE was successful in most patients with tumours for RLS and SS

Table 2 Tumour-associated impact factor analysis for 2D-SWE parameters (n = 78, kPa)

Variable	PLS-1	PLS-2	RLS	SS	p value[d]
All subjects (n = 78)	14.6 (12.8–18.7)	11.8 (9.3–14.7)	9.8 (7.4–12.0)	20.5 (18.0–22.8)	<0.001
Tumour size (maximum diameter)					
1–4 cm (n = 20)	15.2 (12.8–21.6)	12.5 (9.9–16.9)	10.3 (7.8–17.2)	20.9 (18.2–22.6)	<0.001
4.1–6 cm (n = 23)	15.2 (13.0–17.8)	11.8 (8.9–14.1)	8.4 (7.0–11.6)	21.1 (18.4–24.0)	<0.001
6.1–10 cm (n = 21)	14.5 (11.1–19.0)	11.7 (8.8–15.7)	9.9 (7.4–13.1)	20.5 (16.8–25.7)	<0.001
>10 cm (n = 14)	14.5 (12.2–16.5)	10.6 (9.2–12.4)	8.5 (7.2–10.0)	19.8 (17.2–21.7)	<0.001
p value[a]	0.617	0.558	0.350	0.862	-
Tumour location					
Left lobe (n = 16)	15.7 (12.8–18.8)	12.4 (9.0–14.8)	8.4 (7.3–13.1)	19.2 (15.7–22.7)	<0.001
Right lobe (n = 57)	14.5 (13.0–18.9)	11.8 (9.6–15.0)	9.9 (7.5–12.1)	20.6 (18.4–23.5)	<0.001
Both lobes (n = 5)	13.2 (11.2–15.1)	11.0 (9.1–13.4)	9.9 (6.8–12.0)	20.6 (15.3–22.4)	0.001
p value[b]	0.468	0.723	0.919	0.507	-
Tumour type					
HCC, CCC or mixed HCC and CCC (n = 69)	14.7 (12.8–19.0)	11.8 (9.6–15.2)	10.0 (7.6–12.6)	20.6 (18.2–23.3)	<0.001
Other types (n = 9)	13.8 (11.2–17.6)	11.2 (8.4–13.2)	6.3 (5.7–7.7)	18.8 (15.7–21.3)	<0.001
p value[c]	0.348	0.122	0.021	0.348	-

PLS-1 peritumoural liver stiffness measured at 0–1 cm from the tumour edge, *PLS-2* peritumoural liver stiffness measured at 1–2 cm from the tumour edge, *RLS* remnant liver stiffness, *SS* spleen stiffness, *HCC* hepatocellular carcinoma, *CCC* cholangiocellular carcinoma

[a] p values were calculated for the comparison among different sizes of liver tumours

[b] p values were calculated for the comparison among different locations of liver tumours

[c] p values were calculated for the comparison between different types of liver tumours

[d] p values were calculated for the comparison among PLS-1, PLS-2, and RLS

measurements (92.4% and 95.2%, respectively), despite liver fibrosis severity, whereas the success rate in both liver and spleen was a bit higher (97%) in previous research in patients without liver tumours [29]. As expected, PLS obtained at the peritumoural parenchyma had a lower success rate (61.4%) than RLS and SS. These results indicate that lower success rate of PLS was related to the present of tumours. Previous studies have demonstrated that LS should be measured in a well-visualised isoechoic area of the right lobe, free of the liver capsule, ligaments, large vessels, nodule and gallbladder [33, 34]. However, tumours in the right liver lobe might limit the ideal area of measurable liver parenchyma, while tumours in the left lobe might result in unreliable measurements of PLS through subcostal approach. In addition, poor imaging at the peritumoural area could also affect the success of PLS measurement due to lateral or posterior acoustic shadow.

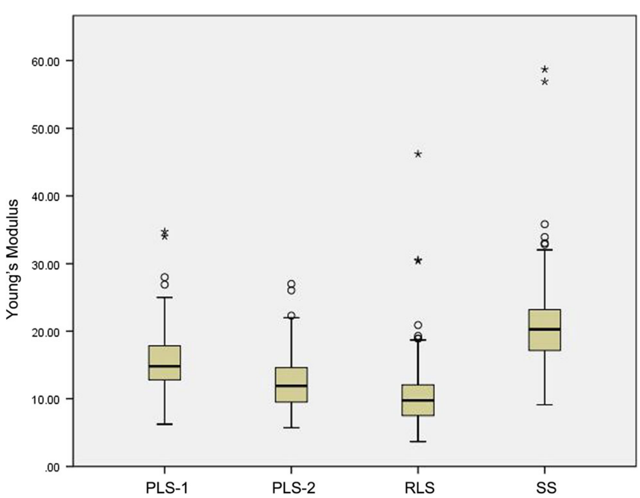

Fig. 3 Box-and-whisker plot showing the mean 2D-SWE values for different elasticity values. The *central box* represents values from the 25th percentile to the 75th quartile, and the *middle of the box* represents the median. *Error bars* show minimum and maximum values (*2D-SWE* two-dimentional shear wave elastography, *SS* spleen stiffness, *RLS* remnant liver stiffness, *PLS-1* peritumoural liver stiffness measured at 0–1 cm from the tumour edge, *PLS-2* peritumoural liver stiffness measured at 1–2 cm from the tumour edge)

Further analyses were performed in our study to determine the impact of tumour-associated factors on 2D-SWE in background liver parenchyma. Tumour size and location showed no impact on each value of stiffness. However, pathological types of liver tumours might be associated with LS measurements because most HCCs or CCCs occurred in fibrotic or cirrhotic livers, whereas most benign lesions and hepatic metastases occurred in normal livers. Although obstructive jaundice caused by tumours, especially CCCs, may increase liver stiffness, there was no such

Table 3 Summary of 2D-SWE values at different sites according to fibrosis stage in all patients (kPa)

Parameter	Elasticity value	Stage S0–S1	Stage S2–S3	Stage S4	p value[a]
PLS-1 (n = 78)	14.8 (12.8–18.2)	13.1 (9.9–14.8)	13.8 (10.5–15.3)	16.1 (14.2–22.0)	<0.001
PLS-2 (n = 78)	11.9 (9.4–14.6)	8.5 (8.2–11.8)	9.6 (8.6–12.0)	13.2 (11.7–17.4)	<0.001
RLS (n = 127)	9.8 (7.5–12.1)	6.3 (5.7–7.1)	8.0 (7.2–9.4)	11.9 (10.0–15.9)	<0.001
SS (n = 127)	20.2 (17.0–23.3)	17.7 (14.7–20.4)	19.7 (16.7–22.3)	21.6 (18.8–25.3)	0.001

Data are presented as medians, with interquartile ranges *in parentheses*

PLS-1 peritumoural liver stiffness measured at 0–1 cm from the tumour edge, *PLS-2* peritumoural liver stiffness measured at 1–2 cm from the tumour edge, *RLS* remnant liver stiffness, *SS* spleen stiffness

[a] p values were calculated for the comparison between different fibrosis stages

case in our population. Tian et al [35] and Huang et al [26] reported that the liver parenchyma appeared to be stiffer in primary liver cancers (HCC and CCC) than in other focal liver lesions. This finding is in accordance with those in our patient population for RLS measurements (10.0 kPa vs 6.3 kPa, respectively; p = 0.021) but not those in PLS-1 or PLS-2 measurements (14.7 kPa vs 13.8 kPa and 11.8 kPa vs 11.2 kPa, respectively; p > 0.05). This result also suggests that LS measurement in the area surrounding the tumour may be increased by tumour compression.

Given the direct effect of the tumour, position of ROI was evaluated as measurements might vary at different distance from the tumour edge. We investigated three regions of background liver to determine the ideal site for 2D-SWE measurement with tumours. In our study, PLS-1 was higher than PLS-2 and even higher than RLS, suggesting that the closer the ROI is placed to the tumour, the higher the Young's modulus value will be. In clinical conditions, tumour compression, oedema, inflammation, micro-infiltration, satellite nodules, and stromal reactions [36] around the tumour contribute to these results. However, all LS values were correlated to liver fibrosis or cirrhosis. RLS provided a higher AUC for differentiation of cirrhosis (S4) than PLS-1 and -2 (AUC = 0.760 and AUC = 0.833, respectively), and 0.925 for diagnosing advanced fibrosis (stage≥S2), which was also higher than 0.720 and 0.785 for PLS-1 and -2. Moreover, the cut-off values exhibited a decreasing trend as ROIs were being placed farther away from the tumour edge. Compared to the results of a recent 2D-SWE study conducted by Huang et al [26], our study resulted in slightly higher AUCs for LS measured greater than 2 cm from the tumour. Few studies have discussed LS measurements at different tumour distances except for the study by Lu et al [37] by using point shear wave elastography (pSWE). It demonstrated that use of stiffness values measured in the liver parenchyma at more than 2 cm from the lesion allowed better diagnostic performance than did values measured in a region closer to the tumour. This finding is consistent with our data. Nevertheless, in our study, RLS showed greater variation (CV = 50.5%) than PLS-1 and PLS-2 (CV = 33.9% and 34.5%). Although it is inconsistent with the data by Lu et al [37] (66% vs 196% at greater than 2 cm and at 0.5–2 cm from the lesion), it is slightly higher than SWE in the segments IV–VII (CV = 27–47%) and lower than SWE in he segments I–III (CV = 61–65%) in healthy population [33]. Differences in criteria of elastography methods might explain this difference [12].

SS correlated with LS, and both increased with progression of liver fibrosis, which was consistent with previous studies [19, 38]. Liver fibrosis-related haemodynamic alterations—blood

Table 4 Diagnostic performance of elasticity values for liver advanced fibrosis (stage≥S2)

Parameter	Cut-off value (kPa)	AUC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p value
PLS-1 (n = 78)	14.1	0.720 (0.575–0.866)	66.7	65.2	75.0	93.5	28.1	0.016
PLS-2 (n = 78)	9.1	0.785 (0.634–0.936)	82.1	84.8	66.7	93.3	44.4	0.002
RLS (n = 127)	8.3	0.925 (0.879–0.971)	80.6	76.6	100	100	46.8	<0.001
SS (n = 127)	20.5	0.703 (0.589–0.817)	56.6	50.5	86.4	94.7	26.4	0.003

Numbers *in parentheses* are 95% confidence intervals

PLS-1 peritumoural liver stiffness measured at 0–1 cm from the tumour edge, *PLS-2* peritumoural liver stiffness measured at 1–2 cm from the tumour edge, *RLS* remnant liver stiffness, *SS* spleen stiffness, *CI* confidence interval, *AUC* area under the receiver operating characteristic curve, *PPV* positive predictive value, *NPV* negative predictive value

Table 5 Diagnostic performance of elasticity values for liver cirrhosis (stage = S4)

Parameter	Cut-off value (kPa)	AUC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*p* value
PLS-1 (*n* = 78)	15.0	0.760 (0.654–0.865)	70.4	65.9	75.7	76.3	65.1	<0.001
PLS-2 (*n* = 78)	10.9	0.833 (0.742–0.924)	79.0	88.6	67.6	76.5	83.3	<0.001
RLS (*n* = 129)	9.9	0.940 (0.902–0.977)	86.4	82.9	90.3	90.6	82.4	<0.001
SS (*n* = 129)	21.5	0.676 (0.584–0.767)	64.4	52.9	77.4	72.5	59.3	0.001

Numbers *in parentheses* are 95% confidence intervals

PLS-1 peritumoural liver stiffness measured at 0–1 cm from the tumour edge, *PLS-2* peritumoural liver stiffness measured at 1–2 cm from the tumour edge, *RLS* remnant liver stiffness, *SS* spleen stiffness, *CI* confidence interval, *AUC* area under the receiver operating characteristic curve, *PPV* positive predictive value, *NPV* negative predictive value

congestion, increased resistance to splenic vein outflow, increased angiogenesis and fibrogenesis—may lead to splenomegaly, a common finding in patients with cirrhosis [39]. The effect of SS was not obvious during the stages of liver fibrosis but became more apparent at the stage of cirrhosis [19, 40]. Thus, in our study, SS was tested as an alternative for diagnosing cirrhosis in the event of no available tumour-free liver for detection, although the diagnostic accuracy of SS for hepatic cirrhosis (64.4%) was poorer than those of LSs, which was also consistent with a previous study [19].

There were several limitations in our study. Only patients with tumours for which resections were planned were included, which limited the types and numbers of benign tumours and precluded patients who were inoperable due to severe liver damage or portal hypertension. Liver stiffness around CCC and HCC might be different, but it was not evaluated in our study due to the small sample size of CCC. Additionally, our study population was Chinese, most of whom were infected with HBV; the remainder had no history of hepatitis or any other liver damage. Thus, the effect of other factors such as alcohol, fats, medications or other types of hepatitis was not evaluated. Furthermore, inter-observer variability was not tested as all examinations were done by one radiologist.

In conclusion, tumour-associated factors have a certain impact on background LS assessment. For patients with liver tumours, parenchymal measurements should be performed >2 cm from the tumour edge for higher success rates and better diagnostic values. The spleen could be used as an alternative for background LS measurement in the event of no available liver for detection.

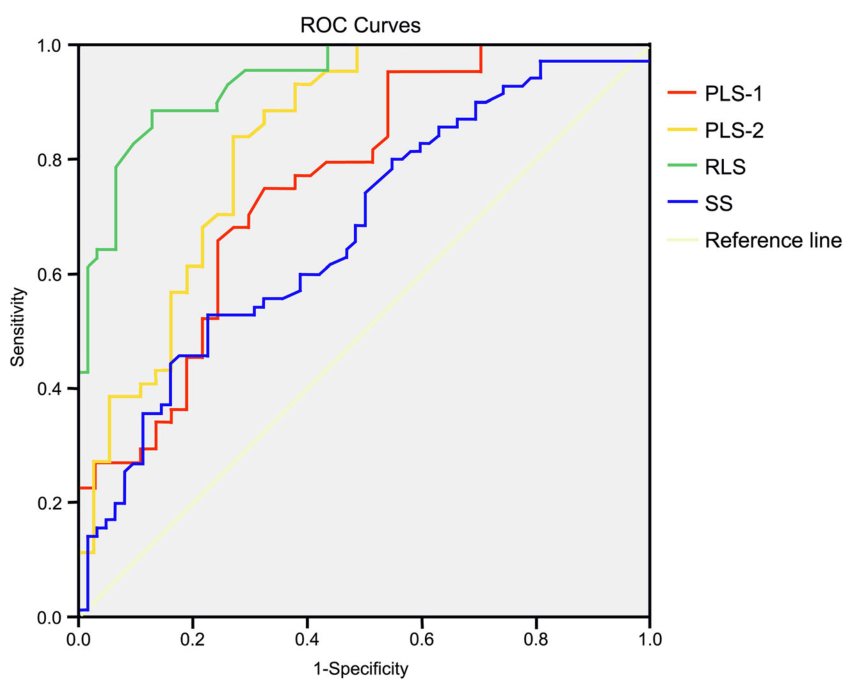

Fig. 4 Graph shows AUC estimations for PLS-1 (*red line*; AUC, 0.760; $p < 0.001$), PLS-2 (*orange line*; AUC, 0.833; $p < 0.001$), RLS (*green line*, AUC, 0.940; $p < 0.001$) and SS (*blue line*; AUC, 0.676; $p = 0.001$). *AUC* area under the receiver operating characteristic curve, *SS* spleen stiffness, *RLS* remnant liver stiffness, *PLS-1* peritumoural liver stiffness measured at 0–1 cm from the tumour edge, *PLS-2* peritumoural liver stiffness measured at 1–2 cm from the tumour edge

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Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Methodology
• prospective
• diagnostic or prognostic study
• performed at one institution

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