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Radio Diagnosis

CLINICAL UTILITY OF LIVER AND TUMOR STIFFNESS MEASURED BY ULTRASOUND SHEAR WAVE ELASTOGRAPHY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED BY THERMAL ABLATION.

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ABSTRACT **AIM :** The aim is to evaluate the utility of liver and tumor stiffness elastography values in predicting the technical success of HCC patients treated by thermal ablation and also to assess the correlation between tumour stiffness elastography values and risk of local tumour recurrence. **MATERIALS AND METHODS:** 50 patients with CHILD PUGH class A liver function and having HCC (less than 3 in number) undergoing thermal ablation for the same were selected.Preprocedurally tumor and liver stiffness elastography values were recorded.All of the patients had atleast one cross sectional imaging followup(CECT/MRI). ROC curve was used to find the ideal cut-off for finding tumor stiffness value, liver stiffness value with respect to recurrence. **RESULTS:** The technical success of thermal ablation for treating HCC in our study was 98%.The association between tumor stiffness elastography value and the risk of developing residual hepatoma was not statistically significant(p value-0.480). The optimal cutoff tumor stiffness value for predicting the development of recurrence was determined as 12.4kPa which was found to be a statistically significant factor for predicting the risk of developing local tumor recurrence(p value of 0.001,sensitivity of 84.21% and specificity of 80.65%,PPV-72.73%, NPV- 89.29% and Accuracy 82%). **CONCLUSION:** Tumor stiffness values obtained by 2D-SWE were found to be a significant predictive factor for the development of recurrence in patients with HCC treated by thermal ablation. Tumor stiffness values obtained by 2D-SWE were not found to be a significant predictive factor for the residual hepatoma in patients with HCC treated by thermal ablation.

KEYWORDS : Elastography, Ablation, Hepatocellular Carcinoma, Liver

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third most common cause of cancer-related death worldwide (1,2). Radiofrequency ablation(RFA) has emerged as an effective local treatment option in patients with cirrhosis and small HCCs <3cm in diameter (2-4). According to AASLD criteria for management of HCC, RFA is recommended for the treatment of <3cm nodule size in cirrhotic patients with Child Pugh A liver function (2,4-8). Microwave ablation(MWA) is a relatively newer ablation technique and offers better ablation outcomes when compared to RFA, especially in tumors which are in proximity to blood vessels (7).

Previous studies investigating the clinical outcome of thermal ablation for HCCs have shown that a patient's underlying liver function can significantly affect overall survival, with many studies reporting that Child-Pugh class B liver function is a significant determinant of poor overall survival after thermal ablation for early stage HCCs (2,4,9,10). The presence of cirrhosis and the degree of liver fibrosis have also been shown to be negative factors for liver regeneration (11). With recent advances in Ultrasound technology, various elastography techniques including transient elastography (TE), point shear-wave elastography (SWE) and two-dimensional (2D)-SWE have been confirmed to be effective tools for staging of liver fibrosis and the diagnosis of liver cirrhosis (12-16). A recent study has tried to analyze the impact of liver stiffness on the survival outcome of patients managed by thermal ablation (17).The objective of this study was to evaluate the utility of liver and tumor stiffness elastography values in predicting the technical success of HCC patients treated by thermal ablation.We also assessed the correlation between tumor stiffness elastography values and risk of local tumor recurrence.

MATERIALS AND METHODS

Institutional Review Board approval was taken for this prospective study. Informed consent was taken from all the patients before they underwent thermal ablation and also prior to recording their tumor and liver stiffness elastography values using ultrasound shear wave elastography.

Patient population

50 patients with CHILD PUGH class A liver function and having HCC (< 5cms and less than 3 in number) undergoing thermal ablation with preprocedural tumor and liver stiffness elastography values were analysed. All the patients had atleast one cross sectional imaging followup (CECT/MRI). CT imaging was performed using 256 slice MDCT (Brilliance-iCT;Philips Healthcare, Cleveland, OH).MRI imaging was performed with 1.5T MR (Imaging HDXT Machine,GE Medical Systems Milwaukee,Wisconsin).Demographic, clinical data , the Child Pugh class, AFP level, PIVKA value,radiological characteristics of the tumors were recorded. 84% of the patients studied were male (42 out of 50), while 16% of the patients studied were female(8 out of 50).The male:female ratio in the study population was 42:8.The average age of the patients included in the study was 67.16 years.

Ultrasound technique

Liver stiffness(LS) and Tumor stiffness(TS) value measurements were performed six times using a convex broadband probe (C5-1; Philips EPIQ 5G) by an abdominal radiologist with five years of experience in

liver US imaging on the same day just before thermal ablation (interval between Shear wave elastography(SWE) and thermal ablation : 0.5-6 hours). LS/TS value measurements were performed on the liver lesion and surrounding liver through the intercostal space/epigastric region in order to ensure a proper sonic window and to avoid any artifacts from cardiac motion. The convex probe was kept still for 5-7seconds during acquisition, and patients were asked to hold their breath during the examination for exact acquisition. A 1.25x0.5cm SWE box was placed in the liver parenchyma to avoid large vessels and the upper edge of the SWE box was placed 1.5-2.0 cm away from the Glisson's capsule. For measuring tumor stiffness, the SWE box was placed within the lesion and care was taken to avoid necrotic/hypoechoic areas and the values were taken from the solid portion of the tumor. For measuring tumor/liver stiffness, the SWE box was considered to have failed when little or no signal was obtained in the SWE box after at least six trials.

Follow up examinations, including contrast enhanced, multiphasic liver computed tomography or MRI, liver function tests and measurement of serum alpha-fetoprotein levels were done in all patients 1 month after thermal ablation. According to the 1-month follow up imaging results, the technical success of the thermal ablation was assessed for each patient.

Technical success was defined as complete ablation observed in the immediate post ablation CECT/MRI done at 1 month follow up. Residual hepatoma was defined as the failure of the ablation zone to completely encompass the tumor seen on CT or MRI obtained before ablation. Local Tumor Progression(LTP)/Recurrence was defined as when a follow-up cross sectional imaging demonstrated findings of interval growth of the tumor along the margin of the ablation zone where the thermal ablation had been considered to be technically effective.

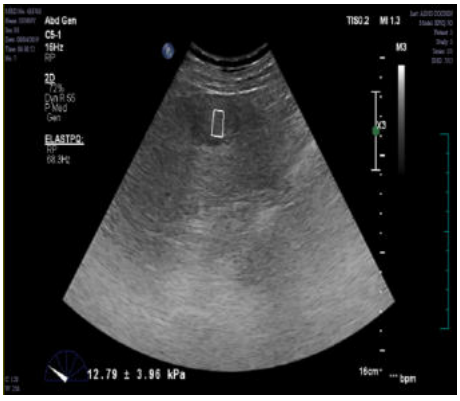

Figure 1.a) showing how TS elastography value was obtained from HCC involving segment 6 of liver.

Figure 1.b) showing how LS elastography value was obtained from liver.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables were expressed using frequency and percentage. Numerical variables were presented using mean and standard deviation. ROC curve was used to find the ideal cut-off for finding tumor stiffness value, liver stiffness value with respect to local tumor recurrence. Diagnostic measures such as sensitivity, specificity, PPV, NPV and accuracy were calculated. Chi square with Fisher exact test was used to find the statistical significance of the association of categorical variables with recurrence. To study the statistical significance of the comparison of continuous variables with recurrence, independent sample t test was applied for parametric data and Mann Whitney u test for non-parametric data. A p value of <0.05 was considered to be statistically significant.

RESULTS

Out of the 50 patients who underwent thermal ablation for HCC, one patient developed residual hepatoma. Hence, the technical success of thermal ablation for treating HCC in our study was 98%. The lesion with the residue had tumour stiffness value of 13.6kPa. However, the association between tumor stiffness elastography value and the risk of developing residual hepatoma was not statistically significant (p value-0.480). This may be because of small sample size.Out of the 50 patients included in our study,19(38%) developed local tumor recurrence. The optimal cutoff tumor stiffness value for predicting the development of recurrence was determined as 12.4kPa (p value 0.001,sensitivity 84.21%, specificity 80.65%). Out of the 22 patients who had tumour stiffness values >12.4kPa, 16 developed (72.72%) recurrence during the study period. Whereas, out of the 28 patients who had tumour stiffness values <12.4 kPa, only 3 developed recurrence (10.7%) in the study period.The association between median tumor stiffness elastography value and recurrence was statistically significant with p value of 0.001,sensitivity of 84.21% and specificity of 80.65%. The Positive Predictive value was 72.73%, Negative Predictive value was 89.29% and Accuracy 82% (Table No.1,Figure 2).

Table No.1: Association between tumor stiffness value and local tumor recurrence

Group	Recurrence (%)	No Recurrence (%)	p value
Median Tumor Stiffness Elastography > 12.4 n=22	16 (72.2)	6 (27.8)	0.001
Median Tumor Stiffness Elastography < 12.4 n=28	3 (10.7)	25 (89.3)	

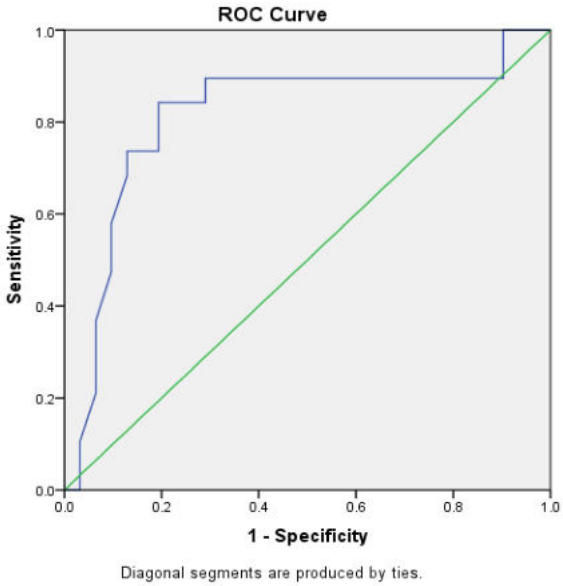

Figure 2: ROC of tumor stiffness value and local tumor recurrence

DISCUSSION

Thermal ablation is the important technique used in treating early HCC in patients with cirrhosis. Response to treatment depends on various patient as well as technical factors. Underlying cirrhosis and the tumour characteristics are critical factors which determine the outcome in these patients.

Previous studies have reported that liver stiffness value measured by 2D-SWE is a significant predictive factor for development of recurrence and overall survival in HCC patients treated with thermal ablation.(17, 18). In our study, the technical success of thermal ablation for treating HCC was 98%. We encountered tumor residue in only one patient in the immediate post procedural CT. These results are

comparable to other studies evaluating technical success of thermal ablation. A study by Lee et al reported a technical success rate of 97% (131 out of 134 patients with HCC ablated using RFA)(17). The lesion with the residue had tumour stiffness value of 13.6kPa. This lesion was located in segment 8 adjacent to branch of right portal vein. However, the association between tumor stiffness elastography value and the risk of developing residual hepatoma was not statistically significant. This may be because of small sample size.

We observed that tumor stiffness values (TS) of the lesions measured by 2D-SWE was a significant predictive factor for development of recurrence. The optimal cutoff tumor stiffness value for predicting the development of recurrence was determined as 12.4kPa (p value 0.001,sensitivity 84.21%, specificity 80.65%).

However, the association between median liver stiffness elastography value and recurrence was not found to be statistically significant (with p value of 0.093).This is probably secondary to a small sample size.

There have been very few studies analysing the association between tumor stiffness and heat dissipation after thermal ablation. A study by RhuiZang et al on mice models showed that increased matrix stiffness leads to increased motility and progression of sublethal heat treated residual HCC cells by activation of extracellular-signal-regulated kinase (ERK) pathway and leads to development of recurrence (19), lending further support to our hypothesis that raised tumor stiffness elastography values are a significant predictive factor for development of tumor recurrence,in HCC patients treated with thermal ablation.

CONCLUSION

In conclusion, Tumor stiffness values obtained by 2D-SWE were found to be a significant predictive factor for the development of recurrence in patients with HCC treated by thermal ablation. Tumor stiffness values obtained by 2D-SWE were not found to be a significant predictive factor for the residual hepatoma in patients with HCC treated by thermal ablation.

List of Abbreviations

LS - Liver Stiffness
TS - Tumor Stiffness
HCC - Hepatocellular carcinoma
TE - Transient Elastography
SWE - Shear wave Elastography
RFA - Radiofrequency ablation
MWA - Microwave ablation
ROC - Receiver Operating Characteristic curve
AASLD - American Association for the Study of Liver Diseases
AFP - Alpha-fetoprotein
PIVKA - Protein induced by vitamin K absence-II
CECT - Contrast Enhanced Computed Tomography
MRI - Magnetic Resonance Imaging
PPV - Positive Predictive Value
NPV - Negative Predictive Value

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