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ENDOSCOPIC ULTRASOUND ELASTOGRAPHY IN ASSESSMENT OF LYMPH NODES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA PREPARED FOR LIVING DONOR LIVER TRANSPLANTATION

By
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Abstract

Lymph nodes are the most frequent site of extrahepatic metastases for hepatocellular carcinoma (HCC). Lymph node metastasis determines patient's management, distinguishing surgical ones from those best suited for non-surgical management. Diagnosis cannot be completely confirmed by imaging and operative exploration. Endoscopic ultrasound elastography (EUS-EG) has a marked role in assessment of lymph nodes in HCC patients and optimizing their management accordingly.

This study assessed diagnostic accuracy of EUS-EG in suspected lymph nodes in HCC potential candidates for living donor liver transplantation (LDLT) and identifued its role in diagnosis and staging of hepatocellular carcinoma.

The study was conducted at the Tropical Medicine department, Ain Shams University, Ain Shams Center of Organ Transplantation (ASCOT) and Endoscopy Unit, Theodor Bilharz Research Institute between July 2018 & May2023. The patients 24 with HCC and abdominal lymphadenopathy were prepared for LDLT. Liver function tests, Positron emission tomography (PET) scan, EUS-EG, EUS- guided fine needle aspiration (EUS-FNA).

The results showed the prevalence of metastatic lymph nodes by EUS-FNA was 41.7%. EUS-EG and PET scan had same sensitivity of 80.0% in detecting metastatic lymph nodes. But, EUS-EG had a higher specificity 85.7% compared to 57.1% specificity of PET scan.

Keywords: HCC, Lymph node metastasis, Living donor liver Transplantation, EUS-EG

Introduction

Hepatocellular carcinoma (HCC) was the 5th common cause cancer in men, the 7th in women, and the 3rd cause of cancer-related death worldwide (Ozakyol, 2017). In Egypt, liver cancer formed 23.81% of total malignancies. HCC constitutes 70.48% of all liver tumors (Forner *et al,* 2012).

Surgery is the mainstay of HCC treatment, leading to the best outcomes in well-selected candidates (five-year survival of 60–80%). Liver transplantation (LT) is recommended as the first-line treatment option for HCC within Milan criteria but unsuitable for resection. Tumor vascular invasion and extrahepatic metastases are an absolute contraindication for LT in HCC (EASL, 2018).

Lymph nodes (LNs) are the most frequent site of extrahepatic metastases for primary HCC. LN metastasis often distinguishes surgical candidates from the best suited for non-surgical management (Xia *et al,* 2014). Imagological evaluation and surgical exploration didn't entirely confirm regional lymph node metastasis. 1-2% of its metastases clinically are occulting; histologically positive, but without remarkable lymph nodes (Grobmyer *et al,* 2006). Diagnostic accuracy of positron emission tomography (PET) to assess HCC was limited due to variable FDG uptake in HCC (Kim *et al,* 2015).

Certain known indicators by conventional EUS as hypoechogenicity, rounded shape, sharp borders, and diameter <1 cm referred to the LNs malignant nature. But, other criteria were in benign LNs or absent in early malignant LNs (Cui *et al,* 2013). EUS-FNA was considered as the gold standard for malignant LNs diagnosis, with PPV and specificity about 100%, but FNA was associated

with complications (Hocke *et al,* 2013).

The visualization of tissue elasticity using real-time tissue elastography is a new imaging technique that can be used during ultrasound examination. It reconstructs and converts the deformability of tissues after compression into color signal. Typically, malignant tumors are harder than benign tumors. Blue, green/yellow, and red, respectively, are the hues connected to hard, intermediate, and soft tissues (Sazuka *et al,* 2016).

This study aimed to assess EUS-EG diagnostic accuracy in suspected lymph nodes in HCC potential candidates for living donor liver transplantation (LDLT) and to identify its role in diagnosis and staging of HCC.

Subjects and Methods

Ethical considerations: This study was approved by the Research Ethics Committee of the Faculty of Medicine, Ain Shams University. Informed written consent was obtained from all patients, whose privacy was given a unique identifier code.

Study design, and setting: This prospective study was conducted at Tropical Medicine Department, Ain Shams Center of Organ Transplantation (ASCOT) and the Endoscopy Unit at Theodor Bilharz Research Institute from July 2018 to May 2023, on HCC patients above 18 years old with significantly enlarged abdominal or mediastinal lymph nodes for liver transplantation.

Sample size: Sample size (24 patients) was calculated by PASS 11 program for sample size calculation and assuming sensitivity of ultrasound elastography was 90% in detecting malign- ant lymph nodes with prevalence of malignancy of 50% that was enough to detect sensitivity from 50% to 90% with 80% power and 0.05 significant level (Okasha *et al,* 2018). Patients were diagnosed with HCC candidate for LDLT with abdominal or mediastinal lymphadenopathy by dynamic CT or MRI.

All patients were subjected to history taking, physical examination, and laboratory investigations, including CBCs, liver profile, kidney function, viral markers, and alpha fetoprotein. Besides, radiological assessments including pelviabdominal U.S., dynamic CT or MRI and PET scan were done.

Endoscopic ultrasound (EUS) was carried out for all HCC patients diagnosed and abdominal or mediastinal lymphadenopathy (using imaging such as Dynamic CT or MRCI). Evaluation of hepatic focal lesions (number, site, size, echogenicity, relation to surrounding and cystic or solid), was performed, and presence or absence of vascular invasion was also evaluated. Assessment of suspected lymph nodes was carried out using conventional endosonographic features predictive of LN metastasis (Hypoechoic structure, sharp distinct margin, and roundness diameter <10 mm, loss of hilum and loss of corticomedullary differentiation). Real-time elastography including blue, green/yellow or red colors and EUS-guided FNA were done for all patients with enlarged LNs.

Statistical analysis: Data were analyzed by using Statistical Package for Social Sciences (SPSS Statistics), version 26 for Windows (IBM Corp., Armonk, N.Y., USA). Categorical variables were given as frequencies and percentages. Numerical variables were given as M±S.D or medians and ranges. Comparisons of means between participants with or without co-morbidities were done using student *t*-test. Mann-Whitney test was used for pairwise comparisons as a post hoc analysis if test showed differences between groups. Categorical variables were compared using $\chi 2$ or Fisher exact tests. A P-value < 0.05 was considered significant.

Results

HCC patients were 20males & 4 females with abdominal or mediastinal lymphadenopathy prepared for LDLT, and ages from 50 to 65 years (±57years). HCV (70.8%) was cirrhosis main cause and HCC, followed by HBV and then combined HBV/HCV with (8.3%) for each, but the negative viral markers in was 12.5% of patients.

Candidates for transplantation were critically selected and comorbidities were limited

to twelve diabetes mellitus patients and six hypertension. MELD (Model for end-stage liver disease) score ranged from 3.82-12.09. According to Child-Pugh score, ten patients were categorized as stage A, twelve as stage B & two as stage C.

EUS morphology, EUS-EG & EUS-FNA of lymph nodes showed that porta-hepatis LNS was the commonest enlarged LNs, followed by Para-aortic LNs. 41.67% of examined lymph nodes by EUS-EG and EUS-FNA were metastatic.

There was a significant relation between EUS-FNA and presence of PVT, multiplicity of lymph nodes, median size and SUV value of lymph nodes by PET scan. There was a significancy \between EUS-FNA and EUS-EG assessment of lymph nodes as to its border, echogenicity, loss of cortico-medullary differentiation & hilum. A significant relation was found between EUS-FNA and EUS-EG assessment of the LNs.

PET CT gave accuracy of 0.667 with sensitivity of 80.0%, specificity of 57.1%, PPV of 57.14% and NPV of 80.0%. But, the EUS gave higher accuracy of 0.833 with same sensitivity of 80.0%, higher specificity of 85.7%, PPV of 80.0% and NPV of 85.7%.

Details were given in tables (1, 2, 3, 4 & 5) and figures (1 & 2).

Table 1: Demographics and baseline characteristics of enrolled patients (n=24)

Parameter	N=24
Age (years)	Range: 50-65M Mean ± SD: 57.33±5.38
Male, no. (%)	20 (83.3%)
Female, no. (%)	4 (16.7%)
Virology	
HCV	17 (70.83%)
HBV	2 (8.33%)
Combined HBV/HCV	2 (8.33%)
Negative	3 (12.50%)
Comorbidities, no. (%)	
Diabetes	12 (50.0%)
Hypertension	6 (25.0%)
MELD score	Range: 3.82 - 12.09, Median: 7.16, 95% CI: 5.75 to 9.25
Child-Pugh score, no. (%): A : B : C	10 (41.7%) 12 (50.0%) 2 (8.3%)

SD: standard deviation; CI: confidence interval; MELD: Model for End-Stage Liver Disease

Table 2: EUS morphology, EUS-EG & EUS-FNA of lymph nodes in patients:

EUS	N=24
LNs site	
Porta hepatis	22 (91.7%)
Para aortic	12 (50.0%)
Peri pancreatic	8 (33.3%)
Porto caval	6 (25.0%)
Retro caval	2 (8.3%)
Celiac	2 (8.3%)
Mediastinal	2 (8.3%)
Morphology	
Largest size (mm)	Range: 5 – 50, Median: 24, 95% CI: 14.5 to 42.5
Shape, no. (%): Ellipsoid : Rounded	10 (41.7%) 14 (58.3%)
Border, no. (%): Sharp : Irregular	16 (66.7%) 8 (33.3%)
Echogenicity, no. (%): Hyperechoic : Hypoechoic	12 (50.0%) 12 (50.0%)
Internal Echogenicity, no. (%): Heterogenous : Homogenous	12 (50.0%) 12 (50.0%)
Cortico-medullary differentiation, no. (%): Preserved : Lost	14 (58.3%) 10 (41.7%)
Hilum, no. (%): Preserved : Lost	14 (58.3%) 10 (41.7%)
Elastography, no. (%): Benign : Malignant	14 (58.33%) 10 (41.67%)
EUS-FNA, no. (%): Benign : Malignant	14 (58.33%) 10 (41.67%)

EUS: endoscopic ultrasound; FNA: Fine needle aspiration; LN: lymph node

Table 3: Relation between EUS guided FNA of lymph nodes and PET CT (n=24)

PET CT	FNA		P value
	Negative (n=14)	Malignant (n=10)	
HFLs, no. (%): Single : Multiple	5 (35.7%) 9 (64.3%)	7 (70.0%) 3 (30.0%)	0.186
HFL largest Size (cm)	Range: 2- 7 Median: 3.5 95% CI: 2.8 to 6.0	Range: 1.2- 12 Median: 9.0 95% CI: 3.0 to 11.0	0.158
SUV (HFL)	Range: 1.5- 18 Median: 4.15 95% CI: 2.0 to 17.0	Range: 2.4- 8 Median: 5.0 95% CI: 4.0 to 5.3	
PVT, no. (%): No : Yes	12 (85.7%) 2 (14.3%)	4 (40.0%) 6 (60.0%)	0.019*
Ascites, no. (%): No : Mild : Moderate	12 (85.7%) 2 (14.3%) 0 (0.0%)	2 (20.0%) 6 (60.0%) 2 (20.0%)	0.005*
LNs, no. (%): Single : Multiple	8 (57.1%) 6 (42.9%)	0 (0.0%) 10 (100.0%)	0.003*
Largest size of LNs (mm)	Range: 8- 40 Median: 25 95% CI: 13 to 35	Range: 14- 50 Median: 45 95% CI: 21 to 49	0.046*
SUV value (LNs)	Range: 0.4- 5 Median: 2.6 95% CI: 1.2 to 4.0	Range: 3- 11 Median: 8.0 95% CI: 6.0 to 9.0	0.001*
Malignant LNs, no. (%): Benign : Malignant	8 (57.1%) 6 (42.9%)	2 (20.0%) 8 (80.0%)	0.069

*significant; PET: Positron emission tomography; HFL: hepatic focal lesion; SUV: Standardized uptake value; PVT: portal vein thrombosis

Table 4: Relation between EUS guided FNA, EUS morphology and elastography of lymph nodes (n=24)

EUS	FNA		P value
	Negative (n=14)	Malignant (n=10)	
Largest Size (mm)	Range: 9-35, Median: 18, 95% CI: 17 to 32	Range: 5-50, Median: 50 , 95% CI: 12 to 50	0.286
Shape, no (%): Ellipsoid :Rounded	7 (50.0%) 7 (50.0%)	3 (30.0%) 7 (70.0%)	0.327
Border, no (%): Sharply demarcated : Irregular	6 (42.9%) 8 (57.1%)	10 (100.0%) 0 (0.0%)	0.003*
Echogenicity, no (%): Hyperechoic : Hypoechoic	10 (71.4%) 4 (28.6%)	2 (20.0%) 8 (80.0%)	0.013*
Internal Echogenicity, no (%): Heterogenous : Homogenous	8 (57.1%) 6 (42.9%)	4 (40.0%) 6 (60.0%)	0.408
Corticomedullary differentiation, no. (%): Preserved : Lost	12 (85.7%) 2 (14.3%)	2 (20.0%) 8 (80.0%)	0.001*
Hilum, no (%): Preserved : Lost	12 (85.7%) 2 (14.3%)	2 (20.0%) 8 (80.0%)	0.001*
Elastography, no (%): Benign : Malignant	12 (85.7%) 2 (14.3%)	2 (20.0%) 8 (80.0%)	0.001*

*significant

Table 5: ROC to diagnose accuracy of PET CT & elastography compared to FNA as a gold standard: (n=24)

Variations	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV	Accuracy
PET CT	8	8	6	2	80.0%	57.1%	57.14%	80.0%	0.667
Elastography	8	12	2	2	80.0%	85.7%	80.0%	85.7%	0.833
Combined	10	6	8	0	100.0%	42.9%	55.56%	100.0%	0.667

TP: true positive; TN: true -ve; FP: false +ve; FN: false negative; PPV: +ve predictive value; NPV: -ve predictive value

Discussion

In the present study, of 24 HCC potential candidates for LDLT with abdominal or mediastinal lymphadenopathy, 10 had metastatic LNs by EUS FNA. Comparing patients with malignant lymph nodes by FNA and EUS-EG to those with benign lymph nodes, these patients with malignant lymph nodes showed significant increased median size of largest lymph node by EUS and PET CT. This agreed with Altonbary *et al.* (2018), who found the mean size of lymph nodes was 4.9 &3.7cm in HCC patients with malignant and benign lymph nodes, respective-

ly. Dietrich *et al.* (2015) reported that LN size was not reliable indicator of metastases.

In the present study, HCC patients with malignant lymph nodes by FNA & EUS-EG showed higher SUV values of lymph nodes by PET CT than those with benign lymph nodes. This agreed with Lee *et al.* (2012), who found that higher SUV values of malignant lymph nodes by PET CT was consistent and that the optimal cutoff of average SUV to predict extrahepatic metastases in HCC patients was > 3.4. Abdelhalim *et al.* (2020) reported that when SUV average was < 3.4, possibility of extrahepatic metastases with poor prognosis. This indicated that metastases occurred more frequently in poorly differentiated HCC with more FDG uptake

In the present study, all LNs with positive FNA results for malignancy had sharp borders and sharp borders were 42.9% of patients with negative FNA. This agreed with Choudhary *et al.* (2016), they reported that prevalence of sharp border of LNs was in 53.3% of HCC patients with malignant LNs by FNA, and sharp border in 3.5% of HCC patients with benign LNs by FNA. Also, in the present study, by comparison to benign LNs, most of malignant LNs by FNA and EUS-EG were hypoechoic by conventional EUS. This also agreed with Choudhary *et al.* (2016), who found that 66.6% of malignant LNs by FNA were hypoechoic by conventional EUS, and compared to 7.1% of benign LNs by FNA. Cortico-medullary differentiation and hilum of LNs by conventional EUS was preserved in 85.7% of patients with benign LNs by FNA and EUS-EG, but lost in 80% of patients with malignant LNs by FNA and EUS-EG. Dudea *et al.* (2012) reported EUS criteria of malignant LNs by B mode, sharp demarcated borders, hypoechogenicity, lost demarcation of cortico-medullary and lost hilum due to replacement or effacement of normal lymphatic cells by condensed malignant cells. Also, Okasha *et al.* (2018) reported that 96.6% of malignant LNs had lost differentiation of hilum by conventional EUS but, 59.7% of benign LNs preserved differentiation of hilum.

In the present study, patients with maliganant LNs by EUS elastography have higher levels of alpha fetoprotein (AFP) than those with benign LNs. This agreed with Lu *et al.* (2016) who reported that serum AFP concentration was significantly higher in metastatic HCC patients than that in liver trauma and non-metastasis HCC patients. The results showed that high serum concentration of AFP positively correlated with metastasis of HCC patients. The link between AFP and metastasis in HCC patients can be contributed to the AFP overexpression, which plays a critical role in promoting invasion and distant metastasis of HCC cells by up-regulated expression of metastasis-related proteins. The molecular mechanism of AFP promoted metastasis of HCC cells by activating the PI3K/ AKT signal pathway**.**

In the present study, there was no significant relation between EUS-FNA & PET CT. PET CT has accuracy of 0.667 with sensitivity 80.0%, specificity 57.1%, PPV 57.14% and NPV 80.0%. This more or less agreed with Kawaoka *et al.* (2009), who compared PET-CT, MDCT, and bone scintigraphy efficacy to detect HCC extrahepatic metastases in 34 patients, reported lymph node metastasis with 66.7% sensitivity & 91.7% specificity for PET-CT. In a meta-analysis of three 18F-FDG PET studies on 239 patients by Ho *et al.* (2007); Lin *et al*. (2012) and Seo *et al.* (2015) detected 77% sensitivity and 98%, specificity for diagnosis of extrahepatic metastases in HCC patients. Anis *et al.* (2011) by PET scanning reported high sensitivity in detecting extrahepatic metastases and a low sensitivity for primary HCC This might be due to the fact that normal liver tissue has a relatively high FDG uptake reducing tumor-to-liver standardized uptake value (SUV) ratio (TLR) and made it difficult to visualize tumor lesions (Bernstine *et al,* 2011). But, Lu *et al*. (2019) reported that the extrahepatic metastases usually have a low FDG uptake background to be visualized.

In the present study, significance was bet-

ween EUS-FNA & EUS-EG ($P < 0.01$). The EUS-EG had higher accuracy (0.833) compared to PET scan, with same (80.0%) sensitivity, 85.7% higher specificity, 80.0% PPV and 85.7% NPV. This agreed with Giovannini e*t al.* (2006), who evaluated 31 patients with LNs in various locations. FNAB samples or surgical specimens provided the basis on final diagnosis. Using a color-coded scale with blue for malignant tissue, green for fibrosis, yellow for normal tissue, and red for fat, they reported a sensitivity of 100% and a specificity of 50%. They emphasized to improve specificity, and highlighted the promising result of using EUS-EG to direct the biopsy. Giovannini *et al.* (2009), who used the same real-time elastographic pattern, 101 LNs from 101 (44 benign LNs & 57 malignant LNs) patients using B-mode EUS images, using EUS-FNAB and/or surgical pathology as reference standards, found specificity of 82.5%. Also, sensitivity, specificity, PPV, NPV, & global accuracy by EUS-elastography were significantly higher than the corresponding B-mode EUS images values (91.8%, 82.5%, 88.8%, 86.8%, & 88.1%, opposed to 78.6%, 50.0%, 70.5%, 60.6%, & 67.3% respectively). Besides, Saftoiu *et al.* (2006) studied qualitative pattern and quantitative histogram analysis in EUS-elastography to distinguish between benign and malignant LNs (31 cervical mediastinal, or abdominal LNs patients and 42 LNs ones) reported 91.7% sensitivity, 94.4% specificity and 92.86% accuracy. Also, Xu *et al.* (2011) evaluated accuracy of EUS-elastography by meta-analysis of seven studies that included 431 LNs from 368 patients across 7 studies, found that the combined sensitivity and specificity to differentiate between benign and malignant LNs were 88% (95% confidence interval (CI) 0.83-0.92) and 85% (95% CI, 0.79-0.89), respectively.

Again, Larsen et al. (2012) assessed EUS elastography and SR in diagnosing nodes present with upper gastrointestinal tract malignancies, using surgical pathology as the reference method in 56 LNs, reported that specificity, sensitivity, PPV, NPV, and accuracy values were 85%, 55%, 71%, 74%, & 73%. Moreover, Cazacu *et al.* (2019) studied a total of 45 patients underwent EUS evaluation of 70 LNs (40 benign, 30 malignant), reported EUS-EG had 100% sensitivity, 60% specificity and 100% NPV.

Conclusion

EUS-FNA is considered as the gold standard in diagnosing malignant LNs. EUS-EG can be play a role to stage HCC patients and assess LNs, allowing for the most proper and efficient management of those patients.

CT/MRI, PET & EUS results were consistent in all HCC patients with abdominal or mediastinal lymphadenopathy. EUS-EG diagnosed superior to PET scan. EUS-EG help EUS-FNA to target the most suspicious areas for biopsy to increase its sensitivity.

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Explanation of figures

Fig. 1: Comparison between FNA negative and FNA positive patients regarding border of Lymph nodes by EUS (1/10 patients positive had sharp borders of lymph nodes by conventional EUS. 6/14 patients negative had sharp borders of lymph nodes)..

Fig. 2: Comparison between FNA negative and FNA positive patients as cortico-medullary differentiation of Lymph nodes by EUS (Cortico-medullary differentiation of lymph nodes lost by conventional EUS assessment in 8/10 patients with positive EUS-guided FNA, but preserved in 12/14 patients with negative EUS-guided FNA).