Official Study Title: Role of Endoscopic Ultrasound Guided Fine Needle Aspiration of Portal Vein Thrombus in the Diagnosis and Staging of Hepatocellular Carcinoma.

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Introduction

Portal vein thrombosis (PVT) is being increasingly diagnosed. It has a wide ranging clinical spectrum from being an asymptomatic state to a potentially life-threatening situation. It is not unusual to find it as an incidental finding in the abdominal imaging done for other reasons. It is commonly associated with cirrhosis and abdominal malignancies and also has a strong association with prothrombotic disorders.

A neoplastic thrombus of the portal vein is found in 6.5%–44% of patients with hepatocellular carcinoma (HCC). Bland (Non-malignant) thrombus occurs in patients with and those without malignant disease. Bland thrombus occurs in 4.5%–26% of patients with chronic liver disease and in 42% of patients with HCC. In addition, bland and tumor thrombi can be coexistent.

Presence of neoplastic thrombus serves as an important determinant of tumor staging, as well as prognosis, and influences treatment selection. In some cases, it may be even the initial sign of an undetected HCC. Therefore, the detection of portal vein thrombus and accurate differentiation of bland from neoplastic thrombus are crucial for patient treatment.

Portal vein tumor thrombosis (PVTT) on imaging studies appears as a low-density plug within a dilated main or lobar portal vein. This plug enhances with contrast in the arterial phase on both CT and MRI and may have arterial signal on Doppler US. Non tumor portal vein thrombosis has a similar appearance to PVTT; however, it does not enhance with contrast nor does it have any Doppler signal. Therefore, whenever a PVT enhances with contrast or has a Doppler signal, PVTT remains the diagnosis until proved otherwise.

Since not every PVT in a patient with HCC is a tumor thrombus, since the nature of the thrombus will ultimately determine the course of treatment, and since PVT may be even the initial sign of an undetected HCC, every effort should be made to distinguish between a tumor and a non-tumor PVT. In addition, malignant PVT does not always demonstrate neovascularity and/or enhancement, which makes FNA necessary in order to characterize the nature of the PVT**.**

Sampling of portal vein thrombus with trans-abdominal ultrasound guidance may lead to erroneous results because of inadvertent inclusion of normal hepatocytes or associated liver masses. Further, potential adverse events of trans-abdominal PV sampling include serious biliary and/or vascular injury.

In contrast to the percutaneous approach, EUS provides a unique view and access to the main portal vein. From the duodenal bulb and second part of the duodenum, the portal vein can be visualized from the confluence of the splenic and superior mesenteric veins into the porta hepatis. Periportal collateral vessels or cavernous transformation of the portal vein, which commonly are associated with portal vein thrombosis, are also easily and reliably detected by EUS instruments with color Doppler US capability approach.

With a linear-array echo-endoscope, the portal vein can be punctured easily with a fine needle under direct visualization, while avoiding the adjacent hepatic artery, bile duct, and collateral vessels (if present). Because the approach is not trans-hepatic, it eliminates any need to avoid the primary tumor and any possibility of contaminating the specimen with hepatocytes, as can occur if the needle tracks through the liver parenchyma. Thus, the rate of false-positive diagnoses is likely to be lower with the EUS compared with the percutaneous approach.

Multiple case reports and case series have demonstrated the safety and efficacy of FNA of PVT. The vast majority of the published literature describes percutaneous US-guided FNA of a PVT, with only few reports noting the use of EUS-guided FNA.

Aim of Work

1) To assess the usefulness of using EUS-FNA in determining the percentage error in triphasic abdominal CT in the diagnosis of malignant portal vein thrombus.
2) To assess the ease and safety of EUS-FNA as an invasive maneuver.

Patients:

Study Design:

This is a pilot study that will include 30 patients with liver cirrhosis and portal vein thrombus which don't fulfill the criteria of malignancy by imaging technique. The patients will be involved in the study will be admitted to Specialized Medical Hospital, Mansoura University Hospitals.

Inclusion Criteria:

- Patients with liver cirrhosis and PVT which don't fulfill criteria of malignancy by triphasic CT abdomen defined as, (neovascularity of thrombus, arterial enhancement with rapid washout, direct invasion by adjacent hepatic mass and diameter of thrombus more than 23 mm), either :
- With or without hepatic mass

- Undergone local treatment or surgical treatment following a diagnosis of HCC and develop PVT during their follow up.

Exclusion criteria:

- Uncooperative or excessively apprehensive patient
- Anticoagulation treatment or non-substituted coagulopathy (International Normalized Ratio ≥ 1.5, Platelet count ≤ 50.000 cells/mm^3, heparin administration at therapeutic doses).
- Inhibition of platelet aggregation by clopidogrel and other thienopyridines.
- Contraindications of sedation (Uncontrolled Diabetes Mellitus, Uncontrolled Thyroid Disorders, Pregnancy, Respiratory Embarrassment, Reactional Drugs like Antidepressants and Anti-anxiety Agents).
- Patients fulfilling criteria of malignancy by triphasic CT on abdomen.
- Extra hepatic metastasis of HCC.
- Child-Pugh classification stage C.

Study end-points:

- 24 months from the start of the research.

Methods:

Patients will be included in this study will be subjected to the following:

I. The study will be explained to all participants in the study, and an informed written consent will be obtained from them before starting the study.

II. Medical history:

Detailed history was taken with stress on:

- Signs of cachexia (unintentional weight loss, progressive muscle wasting, and a loss of appetite)
- Low grade fever
- Recent onset fatigue
- Abdominal pain
- Dyspepsia
- Hematemesis and melena
- Back ache

III. Full clinical examination with special stress on:

- Vital signs including: pulse, arterial blood pressure, temperature, respiratory rate.
- Abdominal Lumps and/or tenderness

IV. Laboratory investigations:

Complete blood count, International Normalized Ratio, Liver enzymes, Serum albumin, Serum bilirubin and Serum creatinine.

V. Radiology: Abdominal ultrasound for initial assessment, Abdominal CT (Contrast Enhanced) (Number of HCC nodules if present, diameter of largest HCC nodule in centimeters, nature of PVT, presence of abdominal metastases if present), Non contrast CT chest to exclude pulmonary metastasis, Bone survey to exclude bone infiltrates.

VI. EUS-FNA:

EUS-FNA will be performed in standard fashion. Under EUS guidance, the main, left and right portal veins will be identified. After verifying

flow signal by Doppler, a 25-gauge EUS-FNA needle will be advanced from the duodenal bulb or second part of the duodenum into the portal vein, 1-2 passes through portal vein thrombus will be taken to ensure adequate cellularity for histopathology. The puncture site will be monitored under EUS for complications.

Study outcomes:

Histopathology of biopsies taken from bland portal vein thrombus which diagnosed by triphasic CT abdomen to evaluate the possibility of malignant PVT that was not discovered by imaging technique (Abdominal ultrasound and triphasic abdominal CT).

Sample size:

One of the goals of a pilot study is to identify unforeseen problems.

Malignant PVT may be an unforeseen problem in patients with liver cirrhosis and / or HCC if not detected by imaging modalities.

This small-scale pilot study will examine the practicality and feasibility of EUS in diagnosing malignant PVT not detected by imaging studies.

With a prevalence of 10%, malignant PVT not detected by imaging studies will almost certainly be identified by EUS (with 95% confidence) in a pilot study including 30 participants.

This sample size was calculated by the following formula[1]:

$$n = \frac{\ln(1-\gamma)}{\ln(1-\pi)}$$

Where,

n = Sample size of the pilot study.

ln = Natural logarithm.

γ = Confidence level (chosen as 0.95)

π = probability (chosen as 0.10)

The result was 28.4 rounded to 29 participants.