EUS Guided Fine Needle Aspiration Cytology of Liver Nodules Suspicious for Malignancy: Yields, Complications and Impact on Management

Varayu Prachayakul MD*,
Pitulak Aswakul MD*, Udom Kachintorn MD*

** Siriraj GI Endoscopy Center, Division of Gastroenterology, Department of Internal Medicine, Siriraj Hospital Mahidol University, Bangkok, Thailand*

Objective: *To examine the sensitivity of endoscopic ultrasonography (EUS) guided Fine needle Aspiration of liver nodules in patients suspected of having primary and metastatic malignancy, as well as the sonographic characteristics of liver nodules, complications and impact on long term treatment.*

Material and Method: *The medical records and endoscopic reports of 14 patients, performed by single endoscopist, who underwent EUS guided FNA of liver nodules from January 2009 to December 2010 and who were enrolled in the present study.*

Results: *12 male and 2 female patients were enrolled, aged between 53-82 median 63 years. 21% of the cases were hepatocellular carcinoma. The sensitivity of diagnosis of malignant liver lesions according to cytology was 78.5%. When the clinical course and pathology which indicated atypical cells were combined, the sensitivity was 100% for malignancy. There were no complications after the procedure. The impact on the treatment plan was 64%.*

Conclusion: *The sensitivity for EUS guided FNA for liver nodules which were suspicious for liver malignancy was high. No complications were observed and the pathology results had 64% impact on the treatment plan.*

Keywords: *Endoscopic ultrasonography, Fine needle aspiration, Sensitivity, Complication, Treatment plan*

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Endoscopic ultrasonography is a new method for the evaluation of intra-abdominal organs, especially pancreatobiliary structures, which cannot always be assessed by simple imaging. One of the most common procedures for EUS interventions is Fine Needle Aspiration cytology (FNA) which plays an important role in the diagnosis of pancreatobiliary malignancy[1-5]. In some patients in whom liver masses were detected, the endoscopist could also perform the FNA of the liver lesions in order to obtain a definite diagnosis from this procedure[6,7]. Even though percutaneous liver biopsy is still the main procedure for evaluation of liver nodules, EUS guided FNA of the liver mass could be an alternative method in some particular cases such as left lobe lesions which might be difficult to access by the percutaneous approach, or in patients undergoing EUS examination for other reasons, leading to the incidental detection of liver lesions for which FNA could provide a one step approach for definitive diagnosis. There have been only two studies from Europe and the United States confirming the feasibility and sensitivity of this procedure. The multicenter trial from Europe (2000)[8], reported 167 cases of EUS guided FNA of liver masses which demonstrated a minor complication rate of only 1%. Dewitt et al[9] (2001) also reported 82-92% sensitivity without any significant complications. EUS guided aspiration of liver masses in Thailand is not a common procedure, as only a few endoscopists are capable of performing this intervention and a review of the data related to this specific procedure is therefore merited.

Correspondence to:
Prachayakul V, Division of Gastroenterology, Department of internal Medicine, Faculty of medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.
Phone: 0-2412-1088, Fax: 0-2419-9610
E-mail: kaiyjr@gmail.com

Material and Method

The medical records of fourteen patients who underwent EUS guided Fine Needle Aspiration for cytological examination from January 2009-December 2010, performed by single endoscopist, were retrospectively reviewed. The endoscopic reports, pathology results and the patients' medical records

were reviewed. The present study was approved by Siriraj Institutional Review Board. All patients provided written informed consent to undergo the procedure. Patients were placed in the left lateral decubitus position and were given intravenous sedation with full anesthetic monitoring. Firstly, Curvilinear array echoendoscope (GF UC 140P, Olympus, Tokyo, Japan) was used to find the liver nodules. After that, EUS-FNA was performed with the same echoendoscope using a 22-gauge FNA needle (Echo tip, Wilson-Cook, Winston Salem, NC, USA). Color Doppler sonography was used to exclude intervening vascular structures along the anticipated needle path. 5 ml suction was applied during moving the needle. The aspirated materials were expressed onto the glass slides and two smear preparations were made. Then, the rest of aspirated materials in the needle were kept in the formalin containing bottle for cell blocks. EUS FNA was repeated until the endoscopist believed that adequate tissue sampling was received. Because the authors did not have an on-site cytologist, the slides and aspirated material containing bottle were sent for cytological diagnosis, elsewhere, within 24 hours. The patients' charts were reviewed. In addition to patient demographics, all details regarding clinical presentations, endosonographic findings of the lesions, EUS FNA, endoscopic interventions, subsequent treatments, complications and pathology results were recorded. Follow-up period was considered to have been until the last recorded hospital visit. The authors utilized the final cytology for the present analysis. The cytology specimens in cases of atypical cells were also reviewed by the pathologist (3 of 14 cases). All the patients were followed-up on average for 4.3 months (from 0.5-10 months). The cytopathology was classified into four groups; 1) definite malignancy (the immunohistochemistry was analyzed as necessary), 2) suspicious for malignancy, 3) atypical cells and 4) benign lesions. Complications were defined as any deviation from the clinical course after EUS that was associated with the procedure as observed by endosonographers, the recovery room nurses or reported by the patients.

Statistical analysis

Assuming that the EUS FNA diagnosis of malignancy is the true positive, sensitivity was calculated as the proportion of the patients with cancer in whom EUS FNA was positive for malignancy. For analysis, Continuous variables were summarized as means with standard deviation (SD) and median (range). Categorical variables were summarized as count and percentages. A 95 percent Confidence Interval (CI) was used for sensitivity value.

Results

Patient characteristics

The patients' baseline characteristics are summarized in Table 1. The age range was from 53-82 years (median, 63 years). Most of the patients were male; the male:female ratio was 7:1. Half had some other diseases such as diabetes mellitus, hypertension or coronary vascular disease. All the cases were clinically suspicious for gastrointestinal and pancreatobiliary malignancy, with liver masses detected from imaging such as Computed Tomography (CT scan) or Magnetic Resonance Imaging (MRI). 11 of 14 cases (78.6%) were scheduled for EUS guided FNA of the liver mass. Only three cases were scheduled for EUS guided FNA of other organs such as the pancreas and lymph nodes. 12 patients had left lobe liver lesions (85.7%). Half of the patients in the present study had multiple liver lesions and the other half had a single liver lesion. The size of the masses varied from 1-2 cm in diameter in 5 patients (21.4%), from 2-5 cm (42.9%) in 6 patients and the lesions in the other 3 patients (35.7%) were greater than 5 cm. Most of the lesions in 10 of 14 patients showed hypoechogenicity without any target signs (71.4%) and only two patients (14.3%) had isoechogenicity, while another two patients (14.3%) showed hyperechogenicity.

Cytology results

The cytology results showed 100% adequacy of the FNA specimens. 10 of 14 cases (71.4%) were positive for malignancy, only one case (7.1%) was suspicious for malignancy and three patients (21.4%) showed atypical cellular pattern but were not definite for malignancy. After clinical follow-up of these 14 cases for 4.3 months on average, all were classified as being suspicious for advanced stage malignancy. The sensitivity of the EUS guided FNA of liver masses in the present study was 78.5% (95% CI: 52.4-92.4%) for positive cases (cytology results were positive for malignancy and suspicious for malignancy). But, if the authors considered the cytology results of atypical cell combined with clinical suspicious for malignancy, the sensitivity would be 100% (95% CI: 78.5-100%).

Complications

All the patients were discharged without any complication within 48 hours after the procedures.

Table 1. Baseline characteristics of the patients

Factors	Details	n (%)
Age median (range)	63 (53-82)	
Sex	Male	12 (85.7)
	Female	2 (14.3)
Other diseases	None	7 (50)
	HT	3 (21.4)
	DM	3 (21.4)
	CAD	0 (0)
	CRF	2 (14.3)
	Other	2 (14.3)
Clinical suspicious for malignancy	Hepatocellular carcinoma	3 (21.4)
	Pancreatic cancer	4 (28.6)
	Cholangiocarcinoma	1 (7.1)
	Metastatic cancer	6 (42.9)
EUS was requested for	FNA liver lesions	11 (78.6)
	FNA other organs	3 (21.4)
Location of masses	Left lobe	12 (85.7)
	Right lobe	2 (14.3)
Number of masses	Single	7 (50)
	Multiple	7 (50)
Size of liver masses	Less than 1 cm	0 (0)
	1-2 cm	3 (21.4)
	2-5 cm	6 (42.9)
	More than 5 cm	5 (35.7)
Echogenicity of lesions	Hypoechogenicity	10 (71.4)
	Hyperechogenicity	2 (14.3)
	Isoechogenicity	2 (14.3)

Impact on Patient Management

After the diagnoses were obtained by this method, there was a measurable impact on the treatment in these patients. 4 of them (28.6%) had palliative chemotherapy, 1 (7.1%) underwent Trans Arterial Chemo-Embolization (TACE) and 4 (28.6%) were changed from curative to palliative therapy only. Six patients (42.6%) died during follow-up. Two (14.2%) were lost to follow-up. Two cases (14.2%) deteriorated, but the rest remained clinically stable. The clinical characteristics of all the cases are summarized in Table 2.

Discussion

From the patients' baseline characteristics, there were no specific EUS characteristics for differentiating between primary and metastatic liver cancer; for examples: numbers, size, location or echogenicity of the lesions. So, tissue diagnosis was only needed for definite diagnosis before treatment. Up to the present, percutaneous biopsy is still the main procedure for evaluation of liver nodules. But it is occasionally difficult in certain situations. At this time, EUS guided FNA of the liver lesions could be an alternative method in some particular cases such as left lobe lesions which might be difficult to access by the percutaneous approach. However, there were only limited data about the sensitivity and complications of this procedure from previous studies many years ago. In the present series, the sensitivity of EUS-FNA for the diagnosis of malignancy by cytology was high and in some particular cases such as hepatocellular carcinoma could be definitely diagnosed by cytology in combination with immuno-histochemistry. After long term follow-up of these patients, none was classified as benign disease. If the sensitivity were calculated from the results of positive and suspicious for malignancy only, it would be 78.5%. However, if the authors consider the patients' clinical characteristics together with the cytology results and include the results of group 3 (atypical cells, possible malignancy) to be clinically suspicious for malignancy, the sensitivity would have been 100%. The cytology results influenced the consequent management of almost two third of these patients.

The complication rate quoted in the European

Table 2. Clinical characteristics, diagnosis and managements of the patients

No.	Age	Sex	Diagnosis	Cytology	Management	Impact on Treatment
1	66	M	Pancreatic cancer	Positive for malignancy	Palliative care	Yes
2	71	M	Pancreatic cancer	Positive for malignancy	Palliative care	No
3	57	M	Lung cancer	Suspicious for malignancy	Chemotherapy	Yes
4	63	M	Lung cancer	Positive for malignancy	Palliative care	No
5	66	M	Pancreatic cancer	Atypical cells, possible malignancy	Palliative care	Yes
6	82	F	Metastatic cancer, primary unknown	Positive for malignancy	Palliative care	Yes [D]
7	78	M	Metastatic cancer, primary unknown	Atypical cells, possible malignancy	Palliative care	No [D]
8	56	M	Metastatic prostate cancer	Positive for malignancy	Chemotherapy	Yes
9	66	M	Hepatocellular carcinoma	Positive for malignancy	TACE	Yes
10	53	M	Hepatocellular carcinoma	Positive for malignancy	Palliative care	No [D]
11	55	M	Cholangiocarcinoma	Positive for malignancy	Chemotherapy	Yes [D]
12	57	M	Pancreatic cancer	Atypical cells, possible malignancy	Palliative care	Yes
13	74	F	Metastatic breast cancer	Positive for malignancy	Chemotherapy	Yes [D]
14	60	M	Hepatocellular carcinoma	Positive for malignancy	Palliative care	No [D]

[D]A patient who died during follow-up period

survey was around 4%, including one major complication (death) and several minor complications (bleeding, infection, abdominal pain). The authors, however, did not experience any complications, leading us to consider this to be a safe procedure. Additionally, it is more convenient than percutaneous liver biopsy for patients, in that it is not necessary to place the patients routinely on their right side during the recovery phase. However, the disadvantage of EUS FNA of the liver is the limited depth of penetration of high frequency (7.5-12 MHz) echoendoscopes. Although image resolution is increased at these higher frequencies, the depth of examination is limited to 5 to 6 cm, resulting in the inability to routinely visualize the right lobe of the liver. As a result of this, the authors were unable to perform FNA at the posterior segment of the right lobe.

Conclusion

EUS guided FNA is a new, effective and probably safe procedure for diagnosis of liver masses suspicious for malignancy. The sensitivity in the present study was high. However, EUS guided FNA is in the authors experience still limited in certain aspects and should mainly be considered as an alternative option to percutaneous liver biopsy in lesions of the left lobe of the liver. It should only be undertaken by experienced and well trained endoscopists, in order to minimize the complication rate.

Potential conflicts of interest

None.

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การตรวจเซลวิทยาเนื้องอกตับโดยใช้เข็มขนาดเล็กเจาะดูดผ่านกระเพาะอาหารด้วยกล้องอัลตราซาวนด์สำหรับการวินิจฉัยมะเร็งรวมถึงผลแทรกซ้อนและผลต่อการรักษา

วรายุ ปรัชญกุล, ปิตุลักษณ์ อัศวกุล, อุดม คชินทร

วัตถุประสงค์*: เพื่อศึกษาความไวในการวินิจฉัยมะเร็งตับจากการตรวจเซลวิทยาโดยใช้กล้องอัลตราซาวนด์ รวมถึงภาวะแทรกซ้อน ผลต่อการรักษาผู้ป่วยในระยะยาว และลักษณะเฉพาะทางอัลตราซาวนด์ของมะเร็งตับแต่ละชนิด*

วัสดุและวิธีการ*: ทบทวนเวชระเบียนและบันทึกข้อมูลของผู้ป่วยที่มารับการตรวจเรื่องเนื้องอกในตับด้วยวิธีส่องกล้องอัลตราซาวนด์ และได้รับการตรวจทางเซลวิทยาโดยใช้เข็มขนาดเล็กเจาะดูดเนื้องอกผ่านกระเพาะอาหารที่ทำโดยแพทย์เฉพาะทางโรคระบบทางเดินอาหาร 1 ท่าน ระหว่างเดือนมกราคม พ.ศ. 2552 ถึงเดือนธันวาคม พ.ศ. 2553 เพื่อศึกษาลักษณะเฉพาะทางอัลตราซาวนด์ของก้อนเนื้องอกตับ และประเมินความเพียงพอของเนื้อเยื่อที่ได้ผลตรวจเซลวิทยา ภาวะแทรกซ้อนและผลต่อการวางแผนรักษาผู้ป่วยในระยะยาว*

ผลการศึกษา*: จำนวนผู้ป่วยในการศึกษานี้มีทั้งหมด 14 ราย (ผู้ป่วยชาย 12 ราย, ผู้ป่วยหญิง 2 ราย) อายุมัธยฐาน 64 ปี (พิสัยระหว่าง 53-83 ปี) และผู้ป่วยทุกรายมีอาการแสดงทางคลินิกที่บ่งชี้ว่าเป็นมะเร็ง ผลการศึกษาพบว่าความไวในการวินิจฉัยโรคมะเร็งตับจากการตรวจด้วยกล้องอัลตราซาวนด์ร่วมกับการตรวจเซลวิทยาโดยใช้เข็มขนาดเล็กเจาะดูดเนื้องอกผ่านกระเพาะอาหารสูงถึงร้อยละ 78.5 และเมื่อพิจารณาผลการตรวจทางเซลวิทยาดังกล่าวร่วมกับอาการแสดงทางคลินิกแล้วพบว่าความไวเพิ่มสูงขึ้นถึงร้อยละ 100 และพบว่าร้อยละ 21 เกิดจากมะเร็งตับชนิดปฐมภูมิ ซึ่งลักษณะทางอัลตราซาวนด์ของเนื้องอกที่พบเป็นได้ทั้งแบบก้อนเดียวและหลายก้อน ส่วนใหญ่พบในตับกลีบซ้ายมากกว่ากลีบขวา นอกจากนี้ยังไม่พบภาวะแทรกซ้อน จากการตรวจโดยใช้เข็มขนาดเล็กเจาะดูดเนื้องอกผ่านกระเพาะอาหารในผู้ป่วยศึกษา และการตรวจด้วยวิธีนี้ส่งผลให้มีการเปลี่ยนแปลงแผนการรักษาผู้ป่วยในระยะยาวถึงร้อยละ 64*

สรุป*: การส่องกล้องอัลตราซาวนด์ร่วมกับผลตรวจทางเซลวิทยาที่ได้จากการใช้เข็มขนาดเล็กเจาะดูดเนื้องอกในตับผ่านทางกระเพาะอาหารมีประสิทธิภาพดีมากในการให้การวินิจฉัยก้อนเนื้องอกในตับที่เกิดจากมะเร็งทั้งกรณีของมะเร็งตับปฐมภูมิและมะเร็งที่กระจายมาที่ตับ โดยปราศจากภาวะแทรกซ้อน และยังมีผลเปลี่ยนแปลงการรักษาผู้ป่วยในระยะยาวอีกด้วย*