J Gastroenterol 2009; 44:190–196
DOI 10.1007/s00535-008-2302-6

Journal of Gastroenterology

Endoscopic ultrasound-guided fine-needle aspiration in patients with lymphadenopathy suspected of recurrent malignancy after curative treatment

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Background. The diagnosis of lymphadenopathy after treatment of malignancy is sometimes difficult, especially in patients whose treatment was deemed curative and without local recurrence or those who have increased serum levels of related tumor markers. We aimed to evaluate the effectiveness of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) as a diagnostic tool in patients with lymphadenopathy after curative treatment of malignancy. ***Methods.*** Consecutive patients with mediastinal, intraabdominal, or pelvic lymphadenopathy after curative treatment of malignancy who were referred to our hospital between October 2003 and September 2007 were enrolled in this study. ***Results.*** A total of 62 patients were included. The lymph nodes were located at the mediastinum in 22 patients, intraabdomen in 38 patients, and intrapelvis in 2 patients. From the pathological findings of the FNA sample, 31 patients (50%) were confirmed to have recurrence of the prior malignancy, and 9 patients (15%) were diagnosed as having a different new malignancy. The remaining 22 patients (35%) were shown to have no recurrence or no other malignancies. However, 1 of them was later diagnosed with recurrence by open laparotomy. The overall sensitivity, specificity, accuracy, and positive and negative predictive values of the EUS-FNA were 97%, 100%, 98%, 100%, and 97%, respectively. ***Conclusions.*** Lymphadenopathy after treatment of malignancy is not a definitive sign of recurrence. Therefore, pathological sampling and diagnosis are essential for determining the appropriate treatment. For this purpose, EUS-FNA is a safe, convenient, and minimally invasive procedure with high diagnostic value.

Key words: EUS-FNA, lymphadenopathy, recurrent malignancy

Introduction

Recurrence is the most serious problem for the patients after the treatment of malignancy. If enlarged lymph nodes are detected during the follow-up period, there is a high possibility of tumor recurrence. However, it is not always easy to confirm or deny recurrence, especially in those patients who received curative treatment, because imaging tests and serum tumor markers are not necessarily helpful for the diagnosis. With regard to the treatment strategy, correct diagnosis is essential, and pathological sampling should be performed if possible. For this purpose, open surgery or other procedures such as mediastinoscopy or laparoscopy is sometimes required for mediastinal and intraabdominal lymphadenopathy. However, these procedures are invasive, costly, time consuming, and require manpower.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has been used for sampling intra- and extramural lesions of the gastrointestinal tract, and is now recognized as a safe, convenient, and accurate procedure. With regard to mediastinal or intraabdominal lymphadenopathy, EUS-FNA has been proven to be helpful for nodal staging of malignancy and for diagnosis of lymphadenopathy of unknown etiology. However, very few studies have validated EUS-FNA with a focus on the patients with lymphadenopathy after the treatment of malignancy[1–3]; in particular, there is no report on the patients who received curative treatment. Therefore, we conducted a prospective, consecutive-entry study to evaluate the effectiveness of EUS-FNA in the patients with lymphadenopathy suspected of recurrent malignancy after curative treatment.

Received: June 3, 2008 / Accepted: September 16, 2008
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Patients and methods

Patients

This prospective, consecutive-entry designed study was performed at the First Department of Internal Medicine, Gifu University Hospital, between October 2003 and September 2007. Enrolled patients had mediastinal, intraabdominal, or pelvic lymphadenopathy, and had previous history of curative treatment of malignancy. "Curative treatment" was defined here as a radical surgical resection for solid tumor or chemotherapy with or without radiation therapy that had induced complete remission of lymphoma. All patients were examined for serum tumor markers related to previous malignancy. The additional inclusion criteria were as follows: (1) the lymph nodes of interest were located at sites that could be approached from the esophagus, stomach, duodenum, or rectum based on computed tomography (CT) imaging; (2) local recurrence at the prior lesion was not observed on imaging tests; and (3) if the patient had other lesions that could be approached more easily and safely, they were excluded from this study, and tissue sampling was attempted there.

The study protocol was approved by the review board for human research of Gifu University Hospital. Written informed consent was obtained from each patient at study entry. The study was conducted in accordance with the human and ethical principles of research set forth in the Helsinki guidelines.

EUS-FNA

EUS-FNA was performed by using an oblique-forward-viewing electronic linear scanning video echoendoscope (GF-UC240P-AL5; Olympus Optical, Tokyo, Japan), which was connected to a processor with color Doppler function (SSD-5000; Aloka, Tokyo, Japan). Following EUS evaluation of the lesion, puncture was done under EUS guidance via the esophageal, gastric, duodenal, or rectal wall. The puncture was achieved with a 19-gauge or 22-gauge needle (EchoTip; Wilson-Cook, Winston-Salem, NC, USA) guided by real-time EUS imaging. The aspirated material was treated as we previously described.[4,5] Neither a pathologist nor a cytologist was present on site at our institution. Histological and cytological diagnoses were made based on the findings of hematoxylin and eosin (H&E) and Papanicolaou staining, respectively. Immunohistochemical staining was also added upon request. The procedure was performed on an outpatient basis unless the patient was already hospitalized for other medical conditions. The outpatients were observed for immediate complications in the recovery room for 2 h, and contact was maintained for 24 h after the procedure to monitor any complications.

Data analysis

The primary endpoint of this study was the sensitivity, specificity, accuracy, and positive and negative predictive values, including their associated 95% confidence intervals (95% CI), of EUS-FNA for confirming tumor recurrence. The calculation was conducted with JMP version 7.0 (SAS Institute, Cary, NC, USA). The secondary endpoint was the ratio of the patients diagnosed with another malignancy, as the treatment strategy must be altered in such patients. The final diagnoses were based on pathological findings, clinical symptoms, serological tests, clinical follow-up, and, if available, surgical pathology. Patients diagnosed with benign lymphadenopathy by EUS-FNA were subsequently followed. Nonspecific lymphadenopathy, excluding sarcoidosis, was diagnosed if spontaneous resolution or lack of progression was noted on follow-up imaging studies for at least 6 months without any deterioration of the patient's health condition.

Results

A total of 62 patients, 34 men and 28 women, with a mean age of 65 years, were enrolled in this study. Lymphadenopathy was detected initially by CT in 60 patients and by fluorodeoxyglucose positron emission tomography (FDG-PET) in 2 patients. Twenty patients (32%) had complaints as follows: abdominal discomfort in 9 patients, lumbago in 3, chest discomfort in 2, body weight loss in 2, hoarseness in 2, general fatigue in 1, and jaundice in 1. However, another 42 patients (68%) did not have any clinical symptoms, and their lymphadenopathies were found by periodical follow-up imaging. The locations of the noted lymph nodes were mediastinal in 22 patients, intraabdominal in 38 patients, and pelvic in 2 patients. Prior malignancies are shown in Table 1, and median period from completion of the prior treatment until detection of the lymphadenopathy was 24 months (range, 3–204 months). Tumor markers related to the prior malignancies were elevated only in 16 patients.

Enlarged lymph nodes were detected by EUS in all patients, and EUS-FNA was also successful in all patients. The median long axis of the punctured lymph nodes was 26 mm (range, 9–68 mm), and the median short axis of the lymph nodes was 16 mm (range, 4–66 mm). The puncture was transesophageal in 22 patients, transgastric in 26 patients, transduodenal in 11 patients, transrectal in 2 patients, and transjejunal in 1 patient. The patient who received transjejunal FNA had undergone total gastrectomy with Roux-en-Y reconstruction for gastric cancer. Sampling of material for pathological examination was successful in all cases, and

Table 1. Prior malignancy of the enrolled patients and the number of cases with confirmed recurrence by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)

Prior malignancy	No. of cases	Cases of recurrence confirmed by EUS-FNA
Malignant lymphoma	12	8
Gastric cancer	10	6
Lung cancer	7	4
Colonic cancer	6	1
Uterus cancer	4	2
Rectal cancer	3	1
Breast cancer	3	None
Pancreatic cancer	2	2
Prostate cancer	2	1
Bile duct cancer	2	None
Plasmacytoma	2	2
Others:[a]	9	4
Paget's disease, hepatocellular carcinoma, lingual cancer, esophageal cancer, renal cancer, bladder cancer, ovarian cancer, liver cystadenocarcinoma, pancreatic endocrine carcinoma	(1 each)	(underlined)
Total	62	31

[a] Underlined malignancies in the bottom row had confirmed recurrence by EUS-FNA

the mean number of needle passes was 2.6 (range, 1–3).

The pathological diagnosis by EUS-FNA included adenocarcinoma in 20 patients, malignant lymphoma in 14 patients, plasmacytoma in 2 patients, neuroendocrine tumor in 1 patient, Paget's disease in 1 patient, hepatocellular carcinoma in 1 patient, gastrointestinal stromal tumor (GIST) in 1 patient, noncaseating granuloma in 4 patients, tuberculous caseating granuloma in 1 patient, and nonspecific inflammation in 17 patients. As a result, 40 patients (65%) were diagnosed with malignant lymphadenopathy, and 22 patients (35%) were diagnosed with benign lymphadenopathy (Fig. 1). Of the patients diagnosed with malignant lymphadenopathy, 31 patients (50%) had confirmed recurrence of the prior malignancy (Table 1, Fig. 2), and 9 patients (15%) were diagnosed with different new malignancies (Fig. 3). Median follow-up period after the prior treatment in the patients with confirmed recurrence was 21 months (range, 3–180 months). Characteristics of the patients diagnosed with different new malignancies by EUS-FNA are shown in Table 2. Of 22 patients with benign lymphadenopathy, 4 patients were diagnosed with sarcoidosis and 1 patient was diagnosed with tuberculous lymphadenitis from the pathological and clinical findings as well as blood and bacterial tests. The remaining 17 patients were diagnosed with nonspecific lymphadenopathy. However, in 1 patient among the latter group, the lymph node further increased in size on CT images after 3 months. Laparotomy was performed in this patient, and he was diagnosed with recurrence of the bladder cancer. The remaining 16 patients were followed periodically, but neither an increase in size of lymph nodes nor any new clinical symptoms appeared in a median follow-up of 22 months (range, 6–42 months).

As shown in Fig. 1 (bottom), recurrence of the prior malignancies was finally confirmed in 32 patients (52%), unrelated new malignancies were found in 9 patients (15%), and 21 patients (34%) were diagnosed with benign lymphadenopathy. Serum tumor markers rose in 12 (38%) of 32 patients with tumor recurrence. The overall sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of EUS-FNA for tumor recurrence were 97% (95% CI, 84–99), 100% (89–100), 98% (91–100), 100% (89–100), and 97% (84–99), respectively.

No complications related to the procedure occurred in any patients.

Discussion

After treatment of malignancy, patients are generally monitored by imaging tests and serum tumor markers to detect tumor recurrence. Lymphadenopathy is sometimes found during such follow-up, but it is rather difficult to judge only from imaging or blood tests whether

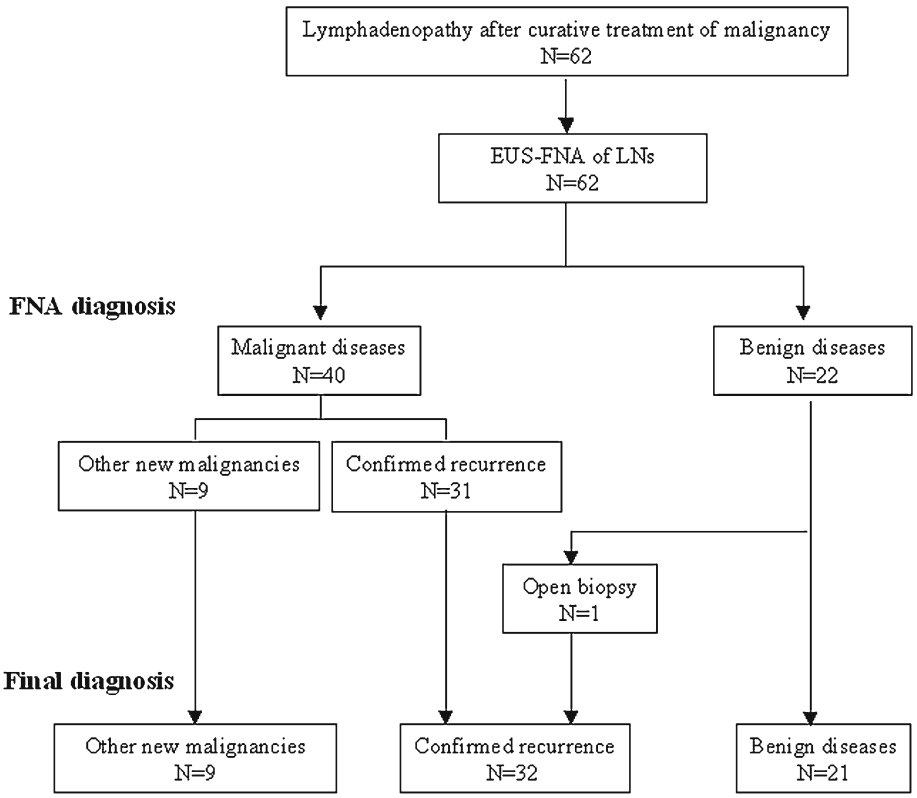

Fig. 1. Flow chart of the diagnostic process

Table 2. Patients diagnosed with different new malignancies by EUS-FNA

	Age/sex	Prior malignancy (histopathology)	Period after treatment (months)	EUS-FNA site	New malignancy (histopathology)
1	83/M	Lung cancer (squamous cell carcinoma)	168	Hepatic LN	Bile duct cancer (adenocarcinoma)
2	84/M	Bile duct cancer (adenocarcinoma)	36	Celiac LN	Malignant lymphoma (follicular)
3	63/F	Uterus cancer (endometrioid carcinoma)	4	Splenic LN	Malignant lymphoma (follicular)
4	80/F	Breast cancer (adenocarcinoma)	139	Mediastinal LN	Malignant lymphoma (DLBCL)
5	75/M	Renal cancer	198	Parapancreatic LN	GIST
6	70/F	Malignant lymphoma (follicular)	48	Mediastinal LN	Lung cancer (adenocarcinoma)
7	76/M	Esophageal cancer (squamous cell carcinoma)	156	Celiac LN	Malignant lymphoma (DLBCL)
8	55/F	Uterus cancer (adenocarcinoma)	156	Superior mesenteric LN	Malignant lymphoma (follicular)
9	72/F	Colonic cancer (adenocarcinoma)	17	Abdominal paraaortic LN	Malignant lymphoma (DLBCL)

LN, lymph node; follicular, follicular B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; GIST, gastrointestinal stromal tumor

the lymphadenopathy indicates a recurrence. If local recurrence at the prior lesion and/or significant elevation of serum tumor marker were observed, the lymphadenopathy would be more likely to result from a recurrence. However, such cases are not so frequent, as indicated in our present study in that the serum tumor marker related to primary malignancy rose only in 12 (38%) of 32 patients with final confirmation of recurrence. Currently, CT is the standard imaging modality for detection of lymph node metastasis, but it provides only limited information such as location and size of the lymph node. Thus, the diagnostic capabilities of CT are not sufficient, and additional imaging modalities are warranted. Recently,[18] F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been introduced for this purpose. It utilizes the increased uptake of glucose by neoplastic tissue, and several studies have demonstrated FDG-PET to be significantly superior to

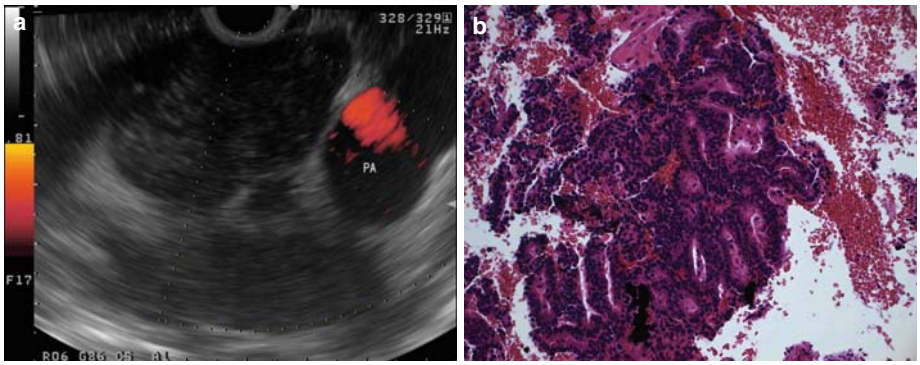

Fig. 2. A 70-year-old man underwent an operation for gastric cancer 3 years earlier. An enlarged lymph node was found in the subcarinal region by follow-up computed tomography (CT). **a** The lymph node was easily detected by endoscopic ultrasound (EUS), and EUS-guided fine-needle aspiration (FNA) was performed via the esophageal wall. **b** Histological findings showed well-differentiated tubular adenocarcinoma, and the patient was finally diagnosed with recurrence of gastric cancer. Hematoxylin and eosin (H&E) ×20

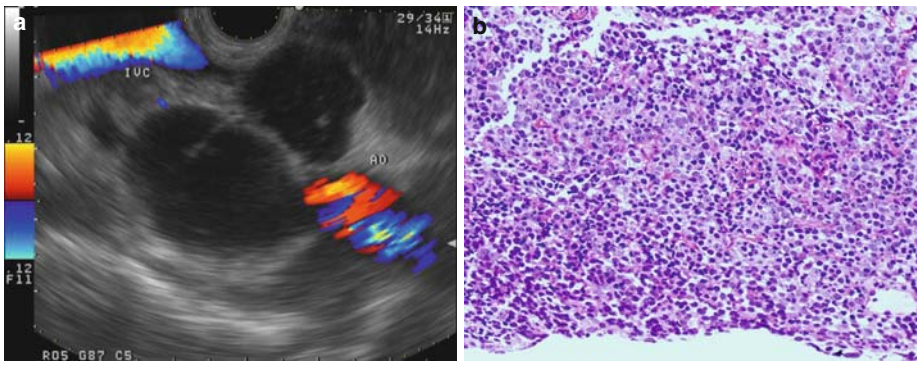

Fig. 3. A 72-year-old woman underwent an operation for colonic cancer 17 months earlier. Enlarged lymph nodes were found in the abdominal paraaortic region. **a** EUS image showed enlarged lymph nodes between the inferior vena cava (IVC) and the aorta (AO), and EUS-FNA was performed to one of the lymph nodes from the descending part of the duodenum. **b** Histological findings showed diffuse proliferation of large neoplastic cells with round or oval nuclei, vesicular chromatin, and one or two nucleoli. H&E stain. ×40. Immunohistological staining showed CD20 positivity, and more than 90% of these cells were also Ki-67 positive. The patient was finally diagnosed with a different new malignancy, diffuse large B-cell lymphoma

CT.[6–8] However, an important issue is that FDG-PET often gives false-positive results because of inflammatory changes and granuloma. In addition, small lymph nodes (<1 cm) and low-grade lymphoma occasionally give false-negative results.[6–8] Therefore, if possible, tissue sampling for pathological confirmation should be conducted before determining the treatment. For this purpose, open surgery or other procedures such as mediastinoscopy and laparoscopy may be required in some cases, although these procedures are invasive, costly, time consuming, and require much manpower.

EUS has also been evaluated as a candidate modality to detect and diagnose lymph node metastasis. Because it delivers a high-resolution image by itself, it can detect small lymph nodes better than CT and FDG-PET. Furthermore, the EUS findings are also helpful for discriminating a malignant tumor from a benign one. On EUS images, a malignant lymph node shows a round shape, with short-axis diameter ≥10 mm, hypoechoic texture, and well-demarcated borders.[9,10] If all four features are present in a lymph node, the possibility of malignancy is 80%–100%.[9,10] However, only 25% of malignant lymph nodes accompany all these characteristics simultaneously.[11] Indeed, in our current study, these four features were found simultaneously in 28 (45%) of all 62 patients, and 24 of the 28 patients had malignancy (86%). However, only 59% of 41 patients were finally diagnosed with malignant lymph nodes. Therefore, although these findings may be useful to differentiate between malignant and benign lymph nodes, the power is still considered insufficient, and pathological diagnosis is still required for determining treatment strategy. Fortunately, another advantage of EUS is the ability to enable simultaneous tissue sampling using the FNA technique. Numerous reports have evaluated the effectiveness of EUS-FNA in the diagnosis of

lymphadenopathy, including preoperative staging of lymph node involvement in non-small cell lung cancer,[12] esophageal cancer,[13] and head and neck cancer.[14] EUS-FNA diagnosis of unknown lymphadenopathy,[15] lymphoma,[4] and several benign diseases such as sarcoidosis[5] and tuberculosis[16] has been also reported. The safety of EUS-FNA has been also established.[17–19] EUS-FNA contains theoretical risks such as bleeding, infection, perforation, and tumor seeding. However, the overall complication rate is not significant (0.3%–1.4%),[17–19] and most of these complications are not serious. From the data of a recent prospective study,[19] 7 of 483 patients (1.4%) developed complications: chest or abdominal pain in 5 patients, self-limited melena in 1 patient, and transient fever in 1 patient. However, no patient was hospitalized for more than 23 h, and the complications were generally mild. Regarding tumor seeding, only 3 cases have been reported so far.[20–22]

Despite the large number of reports about EUS-FNA, few studies have addressed the effectiveness of EUS-FNA with a focus on the lymphadenopathy after treatment of malignancy,[1–3] although the diagnosis is essential for determining the treatment course. DeWitt et al.[2] analyzed the data of patients who had lesions suspected of recurrence after surgery for malignancy. The lesions included 19 masses and only 2 lymph nodes, and they were located in the pancreas in 9 patients, mediastinum in 7, liver in 3, perigastric region in 1, and liver hilum in 1. The cytological diagnosis of recurrent malignancy was made by EUS-FNA in 20 of 21 (95%) patients. A limitation of this study was that only patients with a positive EUS-FNA diagnosis were included.

Kramer et al.[3] assessed 20 patients with mediastinal lymphadenopathy and previous extrathoracic malignancy. The EUS-FNA results were positive for malignancy in 11 patients, negative in 1, and inconclusive in 7. The positive cases included 7 patients with recurrence of primary malignancy and 4 patients with second primary cancers. The overall sensitivity, specificity, and accuracy of EUS-FNA were 69%, 100%, and 75%, respectively. Fritscher-Ravens et al.[1] evaluated the data of 153 patients with mediastinal lymphadenopathy who underwent EUS-FNA. They included 52 patients with previous malignancy, and the cytology revealed recurrences in 21 patients (40%), second primary cancer in 9 patients (17%), and benign lesions in 21 patients (40%); the remaining (1) patient provided inadequate material. The sensitivity, specificity, and accuracy of EUS-FNA in this study were 97%, 100%, and 98%, respectively. The study concluded that benign lesions and treatable second primary cancers occurred with significant frequency, and the authors emphasized the need for tissue diagnosis.

In our current study, recurrence of the prior malignancies was confirmed in 32 patients (52%), another new malignancy was found in 9 patients (15%), and 21 patients (34%) were diagnosed with benign lymphadenopathy. The overall sensitivity, specificity, accuracy, PPV, and NPV of EUS-FNA for recurrence were 97%, 100%, 98%, 100%, and 97%, respectively. Adequate treatments such as chemotherapy and chemoradiation therapy were commenced immediately after the diagnosis in all patients with recurrence as well as in all patients with second primary malignancy.

Lymphadenopathy after treatment of malignancy may not necessarily indicate recurrence. The diagnosis should be determined carefully, especially in cases in which the prior treatment was deemed curative. The lymphadenopathy often has no clinical significance, or it may stem from other new malignancies, as shown in this study. Therefore, pathological sampling and diagnosis are essential for determining the appropriate treatment. For this purpose, EUS-FNA is a safe, convenient, and minimally invasive procedure with a high diagnostic value.

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