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Endoscopic Ultrasound as a First Test for Diagnosis and Staging of Lung Cancer: A Prospective Study

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ABSTRACT

Rationale: Multiple tests are required for the management of lung cancer.

Objectives: Endoscopic ultrasound guided fine needle aspiration (EUS FNA) was evaluated as a single test for the diagnosis and staging (thoracic and extra-thoracic) of lung cancer. **Methods:** Consecutive subjects with CT findings of a lung mass were enrolled for EUS and the results were compared with those from CT and PET scans. **Results:** Of 113 subjects with lung cancer, EUS was performed as a first test (after CT scan) for diagnosis in 93 (82%) of cases. EUS FNA established tissue diagnosis in 70% of cases. EUS FNA, CT and PET detected metastases to the MLN with accuracies of 93%, 81% and 83%, respectively. EUS-FNA was significantly better than CT at detecting distant metastases (accuracies of 97% and 89%, respectively; $p=0.02$). Metastases to lymph nodes at the celiac axis (CLN) were observed in 11% of cases. The diagnostic yields of EUS FNA and CT for detection of metastases to CLN were 100% and 50%, respectively ($p<0.05$). Metastasis to CLN was a predictor of poor survival in subjects with NSCLC, irrespective of size of the CLN. Of 44 cases with resectable tumor on CT scan, EUS FNA avoided thoracotomy in 14% cases.

Conclusions: EUS-FNA as a first test (after CT) has high diagnostic yield and accuracy for detecting lung cancer metastases to the mediastinum and distant sites. Metastasis to the CLN is associated with poor prognosis. EUS FNA is able to detect occult metastasis to the CLN and thus avoids thoracotomy.

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Key words: Lung cancer, Non-small cell lung cancer; Celiac lymph nodes; EUS-FNA; Survival

INTRODUCTION

Lung cancer is the leading cause of cancer death in the United States with an annual incidence of 170,000 cases. [1] A variety of methods are available for cytological or histological diagnosis and pre-operative staging. An ideal test would achieve the cytological diagnosis, stage the tumor with high accuracy and have a low procedure-related morbidity.

Bronchoscopy is commonly used for the cytological or histological diagnosis of lung cancer; however it fails to establish tissue diagnosis in 20-30% of cases. [2] Also, bronchoscopy and the related procedure, transbronchial needle aspiration, play a limited role in staging. [3] Mediastinoscopy has a high accuracy for the detection of metastases to mediastinal lymph nodes. However, it is more invasive, has a complication rate of 1.7%, requires general anesthesia, and plays no role in evaluation of distant sites. [4]

CT scan and CT-guided transthoracic needle aspiration are routinely used for the initial assessment of thoracic/extrathoracic sites and cytological diagnosis, respectively. The limitations are: patients require two visits; there is a high risk of pneumothorax (30%) with 15% requiring chest tube placement [5]; and there is poor sensitivity and specificity for detection of nodal and distant metastases. [6,7] Node positivity on CT is based on the size of the lymph node, which has a poor correlation with the presence of malignancy. [8-]

[12] CT also has a high false-positive rate for detection of distant metastases, particularly in asymptomatic patients. [13, 14]

Fluorodeoxyglucose (FDG)-PET scan, which is based on tumor physiology rather than anatomy, has a higher sensitivity than CT scan for the detection of mediastinal node disease and distant metastases. [15-17] However, the false positivity of the PET scan may be as high as 25%. [18-21]Since surgery is the only chance of cure for NSCLC, positive PET findings that would preclude surgical resection need to be verified.

Endoscopic ultrasound (EUS) with fine needle aspiration (EUS-FNA) has emerged recently as an alternative test for the evaluation of lung cancer. Studies have shown EUS-FNA to be highly accurate in detecting metastases to mediastinal lymph nodes. [22-34] Since fine needle aspiration (FNA) can be performed simultaneously, confirmation of malignancy can usually be accomplished in a single procedure. [35-38] Previous studies of the efficacy of EUS-FNA in diagnosing lung cancer have been conducted on selected populations in which the majority of patients already had the diagnosis of NSCLC established prior to having the EUS procedure. The utility of EUS-FNA for establishing the primary diagnosis in suspicious lung masses and simultaneous thoracic as well as extrathoracic staging remains unknown.

In this prospective study we determined the accuracy of EUS-FNA for the staging (thoracic and extra-thoracic) and the diagnostic yield in unselected consecutive subjects with CT findings of a newly detected lung mass. Some of the results of these studies have been previously reported in the form of an abstracts.[39-44]

METHODS

The institutional review board of Central Texas Veterans Health Care System, Temple, Texas approved this study in March 2004. All the subjects provided written informed consent for both the EUS procedure and participation in the study protocol.

Design

Consecutive patients with newly detected lung mass suspicious for lung cancer or with a recent tissue diagnosis of non-small cell lung cancer (NSCLC) were enrolled in the study. Subjects were excluded if they met any of the following criteria a) advanced heart or lung disease that precludes moderate sedation, b) patient undergoing chemotherapy or radiotherapy for lung cancer, and c) established tissue diagnosis of small cell lung carcinoma (SCLC).

Physicians from primary care, thoracic surgery and sub-specialty clinics (Oncology, Pulmonary) referred patients to Gastroenterology for EUS evaluation. Subjects that met the eligibility criteria were enrolled in the study and were offered EUS-FNA. Other tests for diagnosis (bronchoscopy, transthoracic needle aspiration) and staging (mediastinoscopy/mediastinotomy, PET scan) were performed when clinically indicated. The combination of tests and invasive procedures leading to clinical classification according to the tumor–node–metastasis (TNM) staging system of the American Joint Committee on Cancer [45] was considered traditional staging. A two-stage system was used for staging small cell lung cancer patients. [37]Tumor confined to the lung from which it originated with involvement of the lymph nodes on the same side was categorized as limited stage, whereas cancer that had spread to the other lung, to lymph nodes on the other side of the chest, or to distant organs was defined as extensive stage. [46]

<u>Outcome</u>

The primary outcome of the study was the determination of the accuracy of EUS-FNA for detecting metastasis to mediastinal lymph nodes and distant regions (celiac nodes, liver and adrenal gland) in patients with lung cancer. Since undiagnosed lung mass was an eligibility criterion, the diagnostic yield of EUS-FNA was also obtained. Diagnosis of lung cancer and metastasis to the mediastinal lymph nodes was established cytologically by FNA or by surgically resected sample that showed malignant cells. Surgical exploration and/ or mediastinoscopy was the gold standard for evaluation of the mediastinum. Metastases to distant sites were defined either by the presence of cytologically positive malignant cells or radiological progression of the disease on follow-up imaging studies.

<u>EUS procedure</u>

EUS was done by a single endoscopist. The endoscopist was not blinded to the studies or procedures done up to that point in the evaluation of the patient at the time of referral for the study. The curved linear-array echoendoscope (GF-UCT/P 1140; Olympus

America Corp., Melville, N.Y.) was used for endosonographic examination and fine needle aspiration. EUS examination was done systematically in all patients and included the celiac axis, left adrenal gland, liver (visualized through the stomach and duodenum) and the mediastinal lymph nodes, examined in that order. If a celiac lymph node (CLN) was visualized, FNA was performed irrespective of the endosonographic features and size of the lymph node. The thoracic lymph node stations examined in detail included the paraesophageal, subcarinal, aorto-pulmonary window (station 5) and paratracheal regions.

EUS-FNA was performed using a 22-gauge needle (Olympus FNA needle, Olympus America Corp.). More distant sites of possible metastasis (e.g. CLN, the liver or left adrenal) were always sampled before sampling the mediastinal lymph nodes. A pathologist and cytotechnologist were present in the room to provide immediate interpretation as to whether adequate material was obtained for diagnosis.

<u>CT scans</u>

All CT examinations were performed on-site with the use of a helical CT scanner (model PQ-5000, Picker International, Cleveland). Images were acquired with the use of 10-mm collimation, a table speed of 6.25 mm per second at 175 mA and 120 kV, and a pitch of 1.50. Images were obtained during a single breath-holding session when possible. 100 cc of Omnipaque 300 was administered intravenously to each patient. An injection rate of 3cc/sec and a scan delay of 60-70 sec were used. Lymph nodes were considered enlarged if the short-axis diameter was greater than 1 cm in all mediastinal stations.

Whole-Body PET

PET was performed as part of the routine clinical care with a PET scanner (Siemens, Knoxville TN). After intravenous injection of 18F-fluorodeoxyglucose, transmission and emission scans were performed from the skull base through the inguinal regions. A positive PET scan had at least one hot spot. In selected cases PET was not performed when the tumor was advanced and patients had multiple comorbid illnesses.

Surgery and Mediastinoscopy/mediastinotomy

Surgery was performed by a single surgeon experienced in thoracic oncology. With the exception of stages IIIB and IV, surgery was offered to patients who did not have comorbid illnesses precluding operation. Mediastinoscopy was also performed as part of the preoperative staging to evaluate lymph node levels 1,2,3,4 and 7. Mediastinotomy was also performed for left upper lobe tumors to evaluate lymph node levels 5 and 6. These levels were also explored at the time of thoracotomy with the addition of mediastinal lymph node levels 8 and 9, as well as hilar lymph nodes.

Follow-up visits description and schedule

Follow up consisted of a patient interview by an endoscopy nurse (outpatients) or personal visit by a physician (inpatients), communication with the primary physician, collection of additional radiological test results and review of cytopathologic findings. Follow-up data were gathered 24 hours after the procedure and from clinic visits with the referring physician. Patients in whom the diagnosis of lung malignancy could not be made were followed in the pulmonary or thoracic surgery clinic for repeat CT scans at 3-6 month intervals. Patients were followed to the time of death or to the time of their last visit to their physicians.

Statistics

Sample size assumptions and estimates

The study was designed to detect with a power of 0.80 and a two-sided α level of 0.05, a difference of 20% between the sensitivity of EUS and CT (whose sensitivity was assumed to be 50%) for the detection of metastases to the mediastinum. Assuming metastases to the mediastinum in 60% of the participants, the calculated sample size was 150.

Statistics

Continuous variables are reported as range, mean, and standard deviation. The diagnostic yield of EUS-FNA to establish the tissue diagnosis of lung malignancy was calculated. The primary analysis was comprised of cases where EUS was performed as a first test. The overall analysis was made up of all the cases, irrespective of whether EUS was performed as a first test. Subgroup analysis was performed to determine the diagnostic yield of EUS-FNA in subjects with CT evidence of a normal mediastinum, mediastinal invasion, enlarged mediastinal lymph nodes and/or distant metastases. Sensitivity, specificity, and accuracy of EUS-FNA, CT scan and PET scan for the detection of metastases to the mediastinum and distant sites (celiac axis, liver, and adrenal gland) were calculated and compared. McNemar's test for correlated proportions with the exact test was used to compare the findings of EUS, CT and PET. A p-value <0.05 was considered statistically significant. Survival was measured from the original date of mass detection to the date of death. Data on living subjects were censored at the time of the last clinical follow up. Log-rank tests were used to calculate the median survival time and for the comparison of the survival times between selected groups. Age, histological type, metastases to distant regions (liver, adrenal and celiac axis), surgical treatment and chemo-radiotherapy were used as covariates in the analysis. Cox-proportional hazards model was used to assess the independent predictors of survival. All computations were performed using SAS (Version 9.00, SAS Institute Inc., Cary, NC). Survival analysis was done using *proc lifetest* (for log rank tests) and *proc phreg* (for proportional hazard models). All other computations were carried out using SAS *proc freq*.

RESULTS

Patients

Between March 2004 and July 2005, 157 patients were enrolled in the study. CT scan, EUS and PET scan were performed in 157, 157, and 106 cases, respectively. Of 157 cases, 113 were ultimately diagnosed with lung carcinoma (95 NSCLC and 18 SCLC) and included in the analysis. Forty-four cases were excluded, 21 of them for the following reasons: prior diagnosis of SCLC (2 cases); solitary metastases from melanoma, esophageal carcinoma, renal cell carcinoma, or colon carcinoma (5 cases); surgical confirmation of the benign nature of the lesion (3 cases), stable lesion on follow-up imaging (11 cases). In 12 of the remaining 23 cases, follow-up imaging showed evidence of increased size of the lung mass. Malignancy was suspected, however a definitive diagnosis of malignancy could not be established by the time of study termination and therefore those patients were excluded from the analysis (Figure 1).

Of the 113 cases with lung cancer, EUS was performed as a first test (after CT scan) for diagnosis in 93 (82%) of the cases. In 17 cases (15%) a diagnosis of lung cancer had already been made, and so those patients underwent EUS primarily for staging. However, since 93 (82%) of the 113 patients did not have a prior diagnosis of lung cancer, EUS was the first diagnostic test in the majority of cases. The clinical characteristics of the 113 patients who were evaluated are shown in Table 1.

Diagnosis of lung cancer

The overall diagnostic yield of EUS-FNA as a first test was 70% (95% CI, 60-79%). The diagnostic yields in different subgroups are detailed in Table 2.

Detection of metastases to the mediastinum

Metastases to the mediastinal lymph nodes were established in 49 cases. EUS, CT scan and PET scan detected metastases to the mediastinum with accuracies of 93%, 81% and 83%, respectively.

Detection of distant metastases to the celiac axis, liver and adrenal gland

Celiac Axis

Celiac axis lymph nodes (CLN) were visualized and EUS-FNA performed in 19 (17%) cases. Final diagnoses were as follows: metastatic NSCLC (10), metastatic small cell carcinoma (2), and negative for malignancy (7). Characteristics of the 10 patients with NSCLC metastases are shown in Table 3. The short-axis diameter of the CLN was less than 1 cm in 4 of the cases. The median number of needle passes was 2.5 (range 1-4). The diagnostic yield of EUS-FNA for the detection of the metastases to the CLN was significantly higher than that of the CT scan (100% vs. 50%; $p<0.05$) (Table 4). CT scan missed NSCLC metastases to the CLN in 5 of the 10 cases cytologically proven to be malignant based on tissue obtained by EUS-FNA. The celiac nodes were less than 1 cm in size in 4 of the 5 cases that were missed by CT scan (Table 3). (Figure 2 a, Video clip 1)

An example of a metastasis to the celiac axis identified by EUS-FNA but missed by both CT and PET scans is shown in Figure 2 a.

Univariate analysis of all radiological and endosonographic variables showed that the endosonographic features of large size and hypoechoic celiac lymph nodes were significantly associated with metastases to the CLN ($p < 0.0001$). The same variables were used to fit a multivariate model, and again hypoechoic and large size (>1 cm) lymph nodes were found to be independent predictors of metastasis to the CLN (Table 5). These features both had accuracies of 69% for the diagnosis of malignancy.

Liver

Metastases to the liver were detected in 13 cases (EUS-FNA cytological confirmation in 11 cases; increase in the size of the lesion on the follow-up CT scan in 2 cases). CT scan detected lesions in the liver in 21 of the 113 cases with lung cancer. Thirteen of the 21 cases were ultimately determined to be true metastatic lesions. Of the remaining 8 cases, 6 had a stable lesion on the follow-up CT scans and 2 patients expired within one month and therefore the definite nature of the lesions could not be ascertained. The specificity of EUS-FNA for detection of metastases to the liver was significantly higher than that of the CT scan (p=0.007). There was no significant difference in the overall accuracy of EUS-FNA versus CT (p=0.10). A comparison of the accuracy of EUS-FNA versus PET showed a trend in favor of EUS-FNA (P=0.06) (Table 4).

Adrenal Gland

Metastases to the adrenal gland were detected in 15 cases (EUS-FNA cytological confirmation in 14 cases; increase in size of the lesion on the follow-up CT scan in 1 case). CT reported findings suspicious for metastases in the adrenal gland in 19 cases. EUS-FNA confirmed malignancy in 12 of the 19 cases. Of the remaining 7 cases, one patient died within one month, and follow-up imaging of 6 patients revealed 5 with stable lesions and one with a progressive enlargement. EUS-FNA was performed in 25 cases with lung cancer that had normal appearing adrenal glands on CT scan: two showed malignant cytology. Comparison of the accuracy of EUS versus CT showed a trend in favor of EUS (p=0.07) (Table 4). An example of a metastasis to the adrenal gland that was identified by EUS-FNA but missed by both CT and PET scans is shown in Figure 3.

Distant metastases were detected in a total of 32 of the 113 cases. There was no significant difference in the sensitivity of EUS-FNA, CT scan and PET scan for the overall detection of distant metastases. The specificity and accuracy of EUS-FNA for the detection of distant metastases were significantly higher than those of the CT scan (Table 4). Overall, 40 metastatic lesions were detected in the liver, adrenal gland, and celiac axis in 32 patients with distant metastases. EUS-FNA, CT and PET had sensitivities of 93%, 80% and 50%, respectively for detection of distant metastatic lesions. Celiac metastases were not correlated with the presence of adrenal (p = 0.57) or liver metastases (p = 0.24).

Survival analysis and EUS as a prognosticator

Cox-proportional hazards model showed metastases to the celiac axis and liver to be independent predictors of poor survival (p=0.02) (Table 6; Figure 4).

The median survival time in subjects with and without EUS-evidence of metastasis to the CLN was 142.5 days (95% CI 94,263) and 330 days (95% CI 283, 421). The difference was statistically significant (p=0.002).

A log-rank test showed NSCLC metastases to the CLN, liver and adrenal gland to be associated with poor survival. The median survival in patients with NSCLC metastasis to the CLN was significantly shorter than patients without metastasis to the CLN (5 vs. 10.8 months; p<0.0001). The overall one-year survival in patients with and without metastasis to the CLN was 0% and 42%, respectively. The median survival in patients with and without metastasis to the liver was 7.8 and 10.8 months, respectively (p=0.002), and to the adrenal gland it was 4.4 and 11 months, respectively (p=0.0002).

A stratified analysis on the basis of size of the CLN (less than or more than 1 cm) showed that subjects with metastases to the CLN with either large or small lymph nodes had significantly poorer survival than patients without metastases to the CLN (P<0.01).

There was no significant difference between the survival of patients with enlarged lymph nodes versus small lymph nodes at the celiac axis (p=0.68) (Figure 4).

Impact on treatment

Of 44 cases with resectable tumor on CT scan, EUS-FNA changed the management in 18% (8) cases by upgrading the tumor to stage IV (7%), IIIA to IIIB (7%), and stage II to III A (4%) (Table 7). By using EUS-FNA, thoracotomy was avoided in 13.6% (95% CI, 5-27%) of cases with CT findings of a resectable tumor.

Complications

One patient developed chest pain after EUS guided fine needle aspiration of the pleural effusion. There were no other immediate or late complications due to EUS-FNA.

Discussion

This study showed EUS-FNA to have both a high diagnostic yield and high level of accuracy as a primary test for the staging of lung cancer (thoracic and extra-thoracic) in consecutive subjects with CT findings of a lung mass. EUS-FNA established the primary diagnosis in 70% of the cases with lung tumor. The diagnostic yield was greater than 90% when there was also CT evidence of enlarged mediastinal lymph nodes or distant metastases. EUS-FNA was as accurate as the CT or PET scan for detection of metastases to the mediastinum. The accuracy of EUS-FNA was similar to PET scan and superior to CT scan for detection of metastases to distant regions (celiac nodes, liver and adrenal glands). Importantly, the celiac axis was identified as a common site for distant metastasis, with an incidence of 11%. Patients with metastases to the CLN had a significantly shorter survival, similar to that seen with metastatic disease at other distant sites. EUS-FNA detected occult metastases to the CLN, which were missed in 50% of cases by CT scan. Occult metastasis to the CLN had the same clinical significance as that of overt metastasis. By using EUS-FNA, thoracotomy was avoided in 14% of cases with CT findings of a resectable tumor.

This study found the diagnostic yield of EUS-FNA to be 70%, which is substantially lower than the 90% reported in other studies.[33-35] One possible explanation for this difference is that in the previous studies the patients had tumors or enlarged mediastinal lymph nodes that were located adjacent to the esophagus, whereas in this study we included consecutive patients with a lung mass. Of these lung masses, more than 80% were intraparenchymal (not adjacent to the esophagus) and more than 40% of our patients did not have CT evidence of enlarged lymph nodes. A number of studies have shown that PET is more accurate than CT for the detection of the lung cancers and therefore can be used for diagnosis. However, PET lacks diagnostic specificity for primary and metastatic lesions. [18-21] EUS-FNA offers the distinct advantage of being able to establish both the tissue diagnosis and histological type of the malignancy. Unlike trans-thoracic needle aspiration, which is associated with a high complication rate of 30-45%[5], we did not observe any immediate or late complications as a result of EUS-FNA. The safety profile of EUS-FNA makes it a preferable diagnostic test, particularly since its diagnostic yield is in the same range as those reported for other tests.

The accuracy of the EUS-FNA for the detection of metastases to mediastinal lymph nodes has been reported previously. [22-32] The results of this study are in agreement with previous studies. Stratification into large sized (>1 cm) mediastinal lymph nodes and normal mediastinum revealed that EUS-FNA detected metastases in 60% and 19%, respectively, comparable to previous reports. A 25% false positive rate for the PET scan for metastases to the mediastinum has been reported previously.[18-21] This fact mandates tissue confirmation of metastatic disease before denying a patient attempted surgical cure based on a positive PET scan.

The high incidence (11%) of metastases to the celiac axis was an unexpected and important finding since patients with metastases to the CLN had a significantly shorter survival than patients without CLN involvement. Recently, LeBlanc et al. and Kramer et al. also reported metastases to the CLN in patients with NSCLC. [27,32] However, we found a higher incidence of metastasis because we enrolled both operable and inoperable subjects with advanced-stage lung cancers, and EUS-FNA was performed whenever a lymph node could be visualized at the celiac axis, irrespective of its size or endosonographic features.

This study showed that the diagnostic yield of the EUS-FNA is significantly superior to both the CT scan and PET scan for the detection of metastases to the CLN. A similar finding was reported in subjects with esophageal carcinoma. [47-53] The CT scan requires malignant lymph nodes to be greater than 1 cm in size, and therefore CT will miss micro-metastases that do not result in node enlargement. In this study, in 34% of cases the malignant celiac nodes were smaller than 1 cm. Although PET uses altered cell metabolic activity rather than anatomical size for detection of malignant cells, it is limited to a spatial resolution of about 6 mm. In addition, the scatter effects and motion artifacts secondary to esophageal and stomach peristalsis lower the sensitivity of PET for the detection of microscopic metastases to the upper abdominal lymph nodes. [52,53] Comparative studies have shown a higher diagnostic yield for laproscopy and surgery than for EUS-FNA for metastases to the CLN in esophageal cancer. [54] In our study, since patients with negative celiac nodes did not undergo laproscopic or surgical resection of the CLN, the incidence may be actually higher than 11%.

Metastasis to the CLN as an independent predictor of poor survival is an important finding of our study. This has not been reported before. The median survival in patients with metastases to the CLN was 5 months, which is in the same range as that for metastases to the adrenal gland (4.4 months) and liver (7.8 months). The one-year overall survival in patients with and without metastases to the CLN was 0% and 42%. Forty percent of the CLN metastases were less than 1 cm and were not detected on CT scan. Importantly, occult metastases to the CLN that are not detected by CT scan, but are confirmed to be cytologically malignant by EUS-FNA, have the same clinical significance as large lymph nodes. The median survival in patients with metastases to lymph nodes was 5 months for small nodes and 7 months for large nodes. This highlights a critical role for EUS-FNA, since it is the only test that can both detect sub-centimeter sized lymph nodes at the celiac axis and cytologically confirm the malignant nature of the node.

Currently, EUS is not considered the standard of care for the diagnosis and staging of lung cancer. The results of this study show the celiac axis as a common site for metastases. Therefore, it is important to determine which patients with a diagnosis of NSCLC should undergo EUS evaluation of the celiac axis for complete and accurate staging. Are there clinical or radiological predictors that could define a high-risk group for metastases to the CLN? Of multiple variables, including tumor size, location, and evidence of metastases to mediastinum and other distant sites, there was no significant radiological predictor of metastases to the CLN.

Endosonographic findings of hypoechoic lymph nodes and large size (>1 cm) were independent predictors of metastases to the CLN. However, using size as a criterion, EUS would miss metastases in 40% of the cases, and using hypoechoic lymph nodes, EUS would over-diagnose metastases in 31% of the cases. Different EUS criteria have been studied for the prediction of malignant lymph nodes. In particular size (>1 cm), echogenicity (hypoechoic), margins (sharp) and shape (round) are commonly used for determining metastases to the lymph nodes in the mediastinum as well as in the CLN in patients with esophageal cancer.[18] Both the clinical importance of metastatic microscopic foci at the CLN and the superiority of EUS-guided FNA over endosonographic features shown by other studies[19], suggest that EUS-FNA should be performed regardless of node size once the lymph nodes are visualized at the celiac axis. Absence of metastases to other organs should not deter evaluation of the celiac axis in patients with NSCLC, since celiac nodes may be the only site for distant metastases.

Current staging for lung cancer does not include lymph nodes at the celiac axis as a potential site for distant metastases. Instead, staging is based on imaging studies and mediastinoscopy/ thoracotomy, which are either suboptimal or lack the ability to examine the celiac region. This study shows that evaluation of the CLN region is important for staging for three reasons: 1) metastases to other sites do not predict metastasis to the celiac axis; 2) metastasis to the CLN is associated with poor prognosis independently of metastases to other distant sites; and 3) metastasis to the CLN categorizes the tumor as non-operable. In this study 98% of the subjects were male and 35% had advanced metastasis disease. Additional studies in different group of patients are required to determine the incidence and importance of celiac axis as a site for distant metastases.

EUS-FNA had higher sensitivity than PET and both higher specificity and accuracy than CT for detection of metastases to the liver. The rational for including a liver examination was based on studies that have shown the ability of EUS to detect occult metastases to the liver that are missed by CT scan. [55-57] In this study, 21 cases had CT evidence of lesions in the liver that were suggestive of metastases. EUS-FNA confirmed the cytological diagnosis in 12 of the 13 cases with malignancy. Of the 8 cases with benign lesions, EUS correctly identified all of them as benign. Though CT-guided FNA is available for the same purpose, it requires a second visit and the yield is dependent on the size of the lesion. Since PET lacks the ability to determine anatomical relationships, it misdiagnosed a celiac axis lymph node and a lesion in the right rib as potential liver metastases.

The adrenal glands are a common site for metastases of lung cancer. CT scan of the thorax and upper part of the abdomen has been the standard for assessing the adrenal glands. Since adrenal adenomas are quite common, adrenal masses found in patients being staged for NSCLC are often benign lesions[13, 14] Studies have shown that although PET has a high sensitivity [16] for adrenal metastases, its specificity is low.[13] Since surgery is the only curative option, patients with abnormal imaging results should not be exempted from surgery without tissue confirmation, except when the radiological evidence is overwhelming. This study showed that EUS-FNA has both a high specificity and high sensitivity for adrenal metastases, giving it a higher accuracy than either CT or PET scans. The utility of EUS-FNA for determining metastases to the left adrenal gland was reported earlier in a selected patient population. [58,59] However, our study differs from previous ones because consecutive cases underwent EUS examination of the left adrenal gland and FNA was performed whenever the adrenal gland appeared endosonographically deformed or large, regardless of the CT and PET findings. This approach detected metastases to the adrenal gland in 2 cases that were negative by CT scan and 1 case that was negative by PET scan. The probable explanation of high diagnostic yield of FNA is that micro-metastases to the adrenal gland do not lead to adrenal enlargement and therefore are missed in imaging studies.

In this study, in addition to making a primary diagnosis, EUS-FNA significantly changed patient management in 18% of the 44 patients with resectable NSCLC. In 14% of the cases, in which surgical resection was indicated by CT, thoracic surgery was avoided. This is consistent with findings of previous studies.[25, 27,31], one of which estimated the national cost saving of using EUS-FNA in lung cancer to be approximately $300,000,000 per year, considering a direct cost of $30,000 per thoracotomy and an assumption that 50% of patients with a diagnosis of lung cancer have a normal mediastinum on CT scan in US. [27]

As a result of our study, we recommend that after the initial assessment of the lung mass with a CT scan, EUS-FNA may be considered the next test for establishing the diagnosis and staging of lung cancer, particularly when there is CT evidence of metastases to mediastinum and distant sites. The diagnostic yield of EUS-FNA is in the same range as that of the bronchoscopy with the distinct advantage that thoracic and extra thoracic staging can be performed simultaneously. Bronchoscopy can be reserved for cases with non-diagnostic EUS-FNA and for operable cases, which require accurate endobronchial T-staging. The ability of EUS-FNA to acquire tissue and its high specificity and accuracy for thoracic and extra-thoracic staging makes it preferable to the PET scan. The main limitation of EUS in accessing the pretracheal lymph nodes remains a concern. However, recent studies with endobronchial ultrasound (E-BUS) show that E-BUS in combination with EUS should overcome this shortcoming. [60,61] The high frequency of occult metastases to the CLN found in this study and the high sensitivity of EUS-FNA for their detection represents a distinct advantage of EUS-FNA over other tests. This finding alone argues for EUS-FNA being an integral part of the pre-operative staging of NSCLC.

The limitations of this study were that surgical exploration for verification of EUS-FNA findings was not performed in all cases and a cytopathologic diagnosis of malignancy was the “gold standard” for the diagnosis of malignant lymph nodes and lesions in the distant sites. Because the false positive rate of cytopathology is less than 1%[62], it would be unethical to use other invasive studies, such as surgery, just to confirm the cytopathologic diagnosis of malignancy. Another limitation of the study is that we did not include 44 cases with lung masses in the analysis because tissue diagnosis couldn’t be established. It is possible that up to 12 of these patients ultimately could still prove to have lung cancer, which would decrease the overall diagnostic yield of EUS-FNA.

In this study the definitions of the CLN were not predetermined. During EUS examination the celiac axis was identified and the echoendoscope was rotated clockwise and counterclockwise. If a lymph node could be visualized, it was classified as the CLN. Other investigators have used distance criteria, such as within 2 cm of the origin of the celiac axis irrespective of whether the lymph node is along the celiac axis, gastric artery or hepatic artery. We do not believe that these criteria will have an impact on prognosis and management as long as the nodal metastases have been established outside the thoracic region. In this study we have compared the accuracy of EUS-FNA with PET scans. Recent studies have shown that newer generation combined FDG-PET/CT scanners have a higher accuracy than PET alone because of better lesion characterization and accurate lesion localization. [63] Another possible limitation of the study is that CT examinations were performed with 10-mm collimation, which may have lowered the detection rate in comparison to EUS. It seems logical that with multidetector CT imaging with thinner collimation, the sensitivity to detect smaller lesions may be higher, however, the downside of thinner collimation would be that a greater number of benign lesions would be detected, which would require additional follow up diagnostic studies. The high resolution of EUS and ability to perform EUS-FNA in a single setting is an advantage to characterize such lesions.

In conclusion, EUS-FNA is an excellent test for the diagnosis and staging (thoracic and extra-thoracic) of lung cancer. Importantly, metastasis to the CLN in lung cancer is common and is associated with poor survival. In 50% of NSCLC cases, metastasis to the CLN is not evident on CT scan. Occult metastasis to the CLN detected by EUS-FNA has the same clinical significance as when metastasis is evident by CT. There are no radiological predictors of metastases to the CLN. Absence of metastases to other organs should not deter evaluation of the celiac axis since celiac lymph nodes may be the only region for distant metastases. EUS-FNA is superior to other tests for the detection of occult metastases to the celiac region, which would obviate thoracotomy in patients with otherwise resectable disease.

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Legends

Figure 1. Screening and Enrollment of Subjects for participation in the Study.

Figure 2 a-b. Celiac axis (2 a.) Celiac axis region was normal on CT and PET scans. EUS showed a sub-centimeter hypoechoic lymph node (arrow) measuring 5.7 x 10.3 mm. EUS-FNA confirmed the lymph node to be malignant. (2 b.) Malignant lymph node measuring (16 x 11mm) at the origin of celiac trunk from aorta.

Figure 3 a-b. Left adrenal gland. No abnormalities of the adrenal gland were observed on the CT scan and PET scan. EUS showed a normal sized adrenal gland in one plane (3 a) and a distinct bulge (3 b) in another plane. EUS-FNA of the bulged region of the adrenal gland was positive for malignant cells.

Figure 4 a-c.

Kaplan-Meier curve showing the impact of metastases to the celiac axis lymph nodes on survival.

4 a. Survival in subjects with and without metastases to lymph nodes at the celiac axis. The median survival time in subjects with and without EUS-evidence of metastases to CLN was 142.5 days and 330 days respectively. The difference was statistically significant (p=0.002).

4 b. Modified risk score-adjusted estimated survivor function showing survival in subjects with and without metastases to lymph nodes at the celiac axis after controlling for age and metastases to the liver and adrenal gland. Estimated median survival time is 183 days for those with metastases to the celiac lymph nodes and 330 days for those without metastases to the celiac lymph nodes. The difference was statistically significant (p=0.02).

4 c. Comparison of Survival in Patients with NSCLC metastases to Lymph Nodes at the Celiac Axis (Small vs. Large lymph nodes) vs. Patients without NSCLC Metastases to Lymph Nodes at the Celiac Axis

Video clip 1. Video clip showing longitudinal section of the aorta, origin of celiac trunk and an oval hypoechoic lymph node (8.3 mm in size) at the origin of celiac trunk. EUS-FNA of the lymph node (not shown in the video clip) showed malignant cells.

Table 1.

Demographics and Tumor Characteristics of the 113 patients with Lung Carcinoma

Characteristic	Value
Total number of patients	113
Sex	
Male	111
Female	2
Age (yr)	
Median ± S.D.	66 ± 9.8
Range	45-86
Tumor histology	
NSCLC	95
SCLC	18
Tumor side	
Right-sided	63
Left-sided	46
Both sides	4
Stage	
NSCLC IA	9
IB	4
IIA	1
IIB	6
IIIA	19
IIIB	16
IV	40
SCLC Limited	12
Extensive	6

Table 2.

Sensitivity of EUS–FNA as a Diagnostic Test in Different Subgroups

Subgroups	**Overall Analysis**	
	n	Sensitivity (95%CI)
CT Findings		
Lung mass	113	70% (61-78%)
Normal mediastinum	46	57% (41-71%)
Mediastinal invasion	25	92% (74-99%)
Enlarged MLN	67	79% (67-88%)
Distant metastases (Liver, adrenal, celiac axis)	32	100% (89-100%)
Histological type		
NSCLC	95	65% (55-75%)
SCLC	18	94% (73-100%)

MLN – mediastinal lymph node

Table 3.

Radiological and Endosonographic Findings of NSCLC Metastases to Lymph Nodes at the Celiac Axis

Cases	CT scan	EUS features of the Lymph nodes			EUS-FNA			Distant metastases
		Size* (mm)	Shape	Hypoechoic	Result	Passes	Tissue type	
1.	Positive	32	Round	Yes	Positive	3	NSCLC	
2.	Positive	12	Round	Yes	Positive	2	NSCLC	Adrenal
3.	Positive	16	Round	Yes	Positive	3	NSCLC	
4.	Negative	11	Oval	Yes	Positive	3	NSCLC	
5.	Positive	22	Round	No	Positive	-	NSCLC	
6.	Negative	5.2	Round	Yes	Positive	2	NSCLC	Adrenal/Liver
7.	Positive	16	Round	Yes	Positive	2	NSCLC	
8.	Negative	5.2	Oval	Yes	Positive	1	NSCLC	
9.	Negative	5.4	Round	Yes	Positive	4	NSCLC	
10.	Negative	5.7	Oval	Yes	Positive	2	NSCLC	

* - Short-axis dimension

Table 4.

Comparison of Diagnostic yield, Sensitivity, Specificity, and Accuracy of EUS-FNA, CT scan and PET scan for the detection of Metastases to the Celiac axis, Liver, Adrenal Gland, and Distant metastases (per patient)

	EUS	CT	PET
Celiac axis			
Diagnostic yield	100% (74-100%) [α]	50% (21-79%)	33% (04-78%)
Liver			
Sensitivity	85% (55-98%)	100% (75-100%)	50% (07-93%)
Specificity	100% (96-100%) [α]	92% (85-97%)	95% (88-99%)
Accuracy	98% (94-100%) [Ω]	93% (87-97%)	93% (85-97%)
Adrenal gland			
Sensitivity	93% (68-100%)	87% (60-98%)	75% (19-100%)
Specificity	100% (96-100%) [μ]	95% (89-98%)	98% (91-100%)
Accuracy	99% (95-100%) [μ]	94% (88-98%)	97% (90-99%)
Distant Metastases			
Sensitivity	91% (75-98%)	88% (71-97%)	79% (49-95%)
Specificity	100% (96-100%) [Ψ]	90% (80-95%)	100% (95-100%)
Accuracy	97% (93-100%) [β]	89% (81-94%)	97% (90-99%)

[α] - EUS vs. CT “p” value <0.05
[Ω] - EUS vs. PET “p” value =0.06
[μ] - EUS vs. CT “p” value =0.07
[Ψ] - EUS vs. CT “p” value =0.004
[β] - EUS vs. CT “p” value =0.02

Table 5.

5 a. Univariable Logistic Regression: Predictors of Metastases to Lymph Nodes at the Celiac Axis

Variable	p-value
Age (categorical; >65 years)	0.8864
Radiological (CT scan)	
Mass	
Side (right vs. left)	0.1814
Location (lobes)	0.2175
Number of lesions (1 vs. >1)	0.2963
Size (<2.5 vs. 2.5-5.0 vs.5.0)	0.4013
Mediastinum (enlarged LN)	0.4703
Liver metastases	0.6356
Adrenal metastases	0.4851
Enlarged CLN	0.9077
EUS	
Mediastinal metastases	0.1041
Liver metastases	0.9400
Adrenal metastases	0.3880
Enlarged CLN	0.9984
CLN	
Shape (round vs. oval)	0.9557
Size (>1 cm)	< **0.0001**
Echogenicity	< **0.0001**

5 b. Multivariable Logistic Regression: Independent Predictors of Metastases to Lymph Nodes at the Celiac Axis

Term	Estimate	Lower 95%	Upper 95%	p-value
Intercept	4.67	3.04	7.75	<.0001
Celiac lymph node: size	-3.64	-7.52	-0.91	0.0250
Celiac lymph node: echogenicity	-4.10	-7.30	-1.97	0.0009

5 c. Accuracy of Endosonographic features of Lymph Nodes at the Celiac Axis for Detection of Metastases

	Sensitivity	Specificity	PPV	NPV	Accuracy
Size > 1 cm	60%	83%	86%	44%	69%
Hypoechoic	90%	67%	69%	33%	69%

Table 6.

6 a. Log-Rank Tests showing Impact of Different Variables on Survival

Variable	n	χ^2	"p" value
Age	113	5.15	0.160
Surgery	112	7.19	0.007
Chemotherapy	113	14.99	< 0.001
Metastases to mediastinum	79	10.62	0.001
Liver metastases	113	19.92	< 0.001
Adrenal metastases	113	3.35	0.06
Celiac metastases	113	9.19	0.002
Staging	113	20.79	0.007
Histological type	113	0.13	0.709
Metastases to CLN adjusted to metastases to liver & adrenal gland	113	8.20	0.004
Metastases to celiac axis adjusted for histological type	113	7.19	0.007

6 b. Cox proportional hazards analysis showing independent predictors of survival

Variable	Parameter	Std. error	χ^2	"p" value	Hazard ratio
Surgery	-1.24	0.533	5.408	0.02	0.289
Chemotherapy	-1.22	-1.299	17.190	< 0.01	0.293
Adrenal metastases	-0.37	-0.374	0.870	0.35	0.688
Liver metastases	1.26	0.362	12.115	< 0.01	3.530
Celiac metastases	0.86	0.374	3.307	0.02	2.368

Table 7.

Impact of the EUS-FNA on Management of NSCLC and SCLC by Upgrading the Stage of the Tumor

	Tissue Type	Change in CT staging as a result of EUS-FNA	N
Celiac axis	NSCLC	M0 to M1	3
Mediastinal lymph nodes	NSCLC	N2 to N3 (IIIA to IIIB)	3
Mediastinal lymph nodes	NSCLC	N0 to N2 (II to IIIA)	2
Adrenal gland	SCLC	Limited to Extensive	1
Mediastinal lymph nodes	SCLC	Limited to Extensive	1

Figure 1.
Screening and Enrollment of Subjects for participation in the Study.

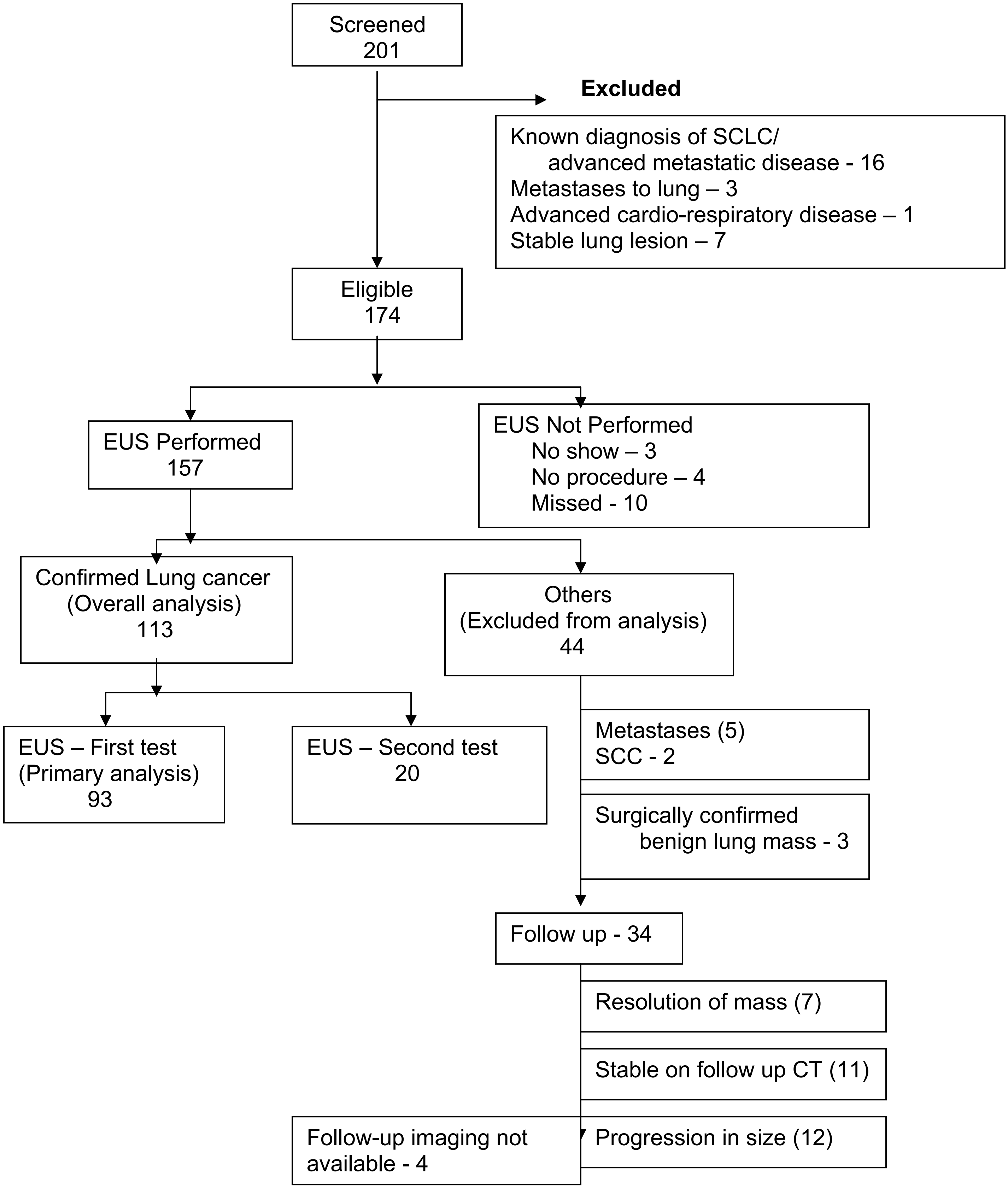


Figure 2. Celiac axis

Figure 2 a.

Figure 2 b.

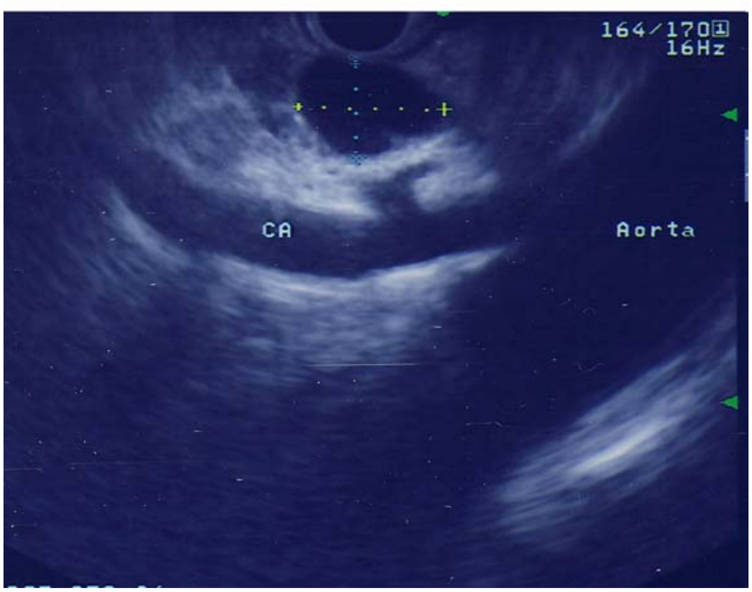


Figure 3.

Figure 3 A.

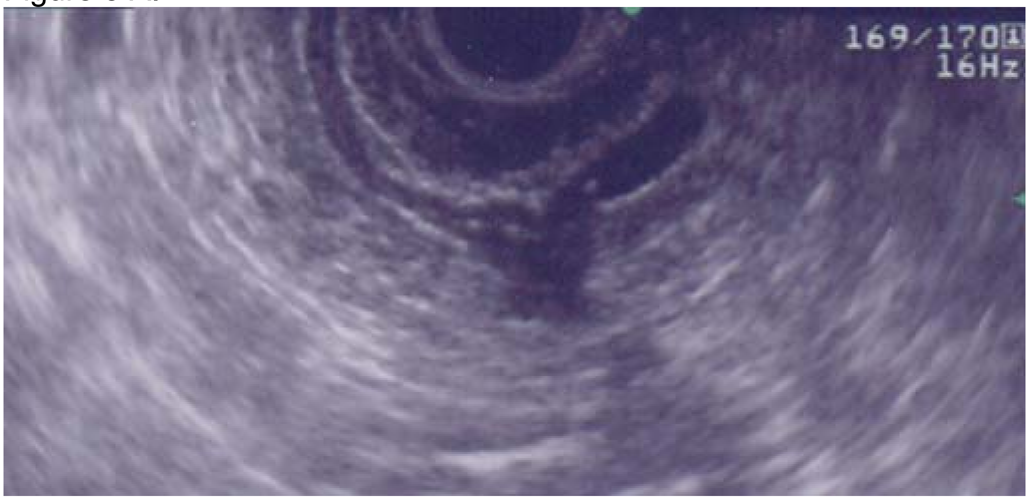
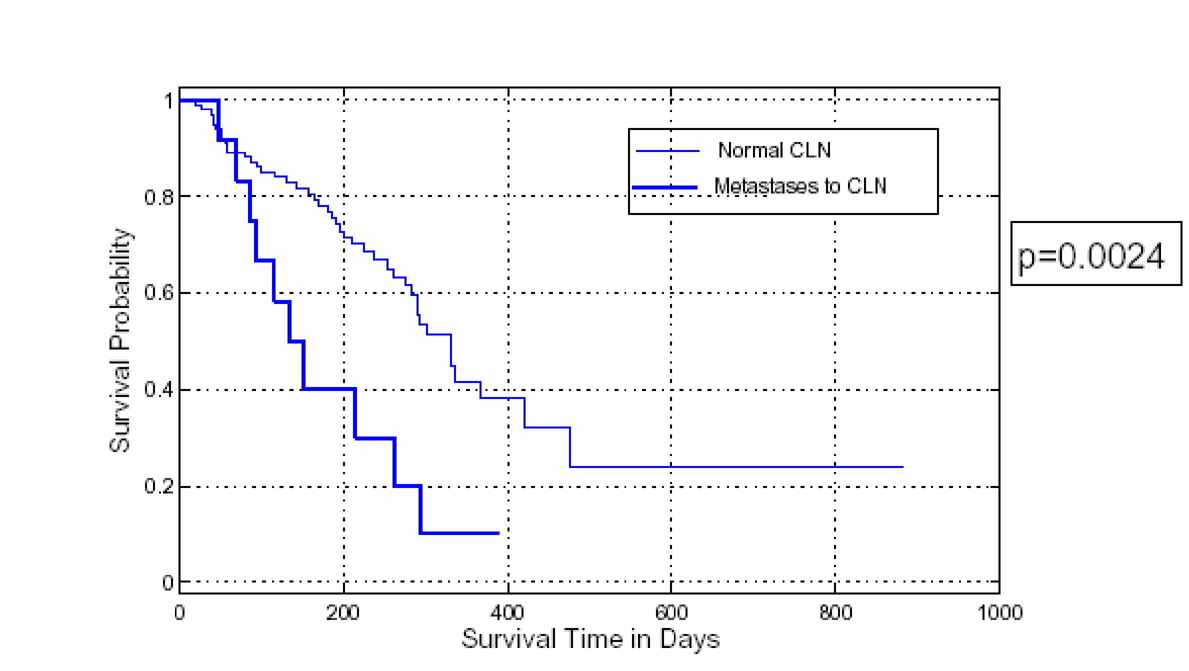


Figure 3 B.

Figure 4.

4 a.



4 b.

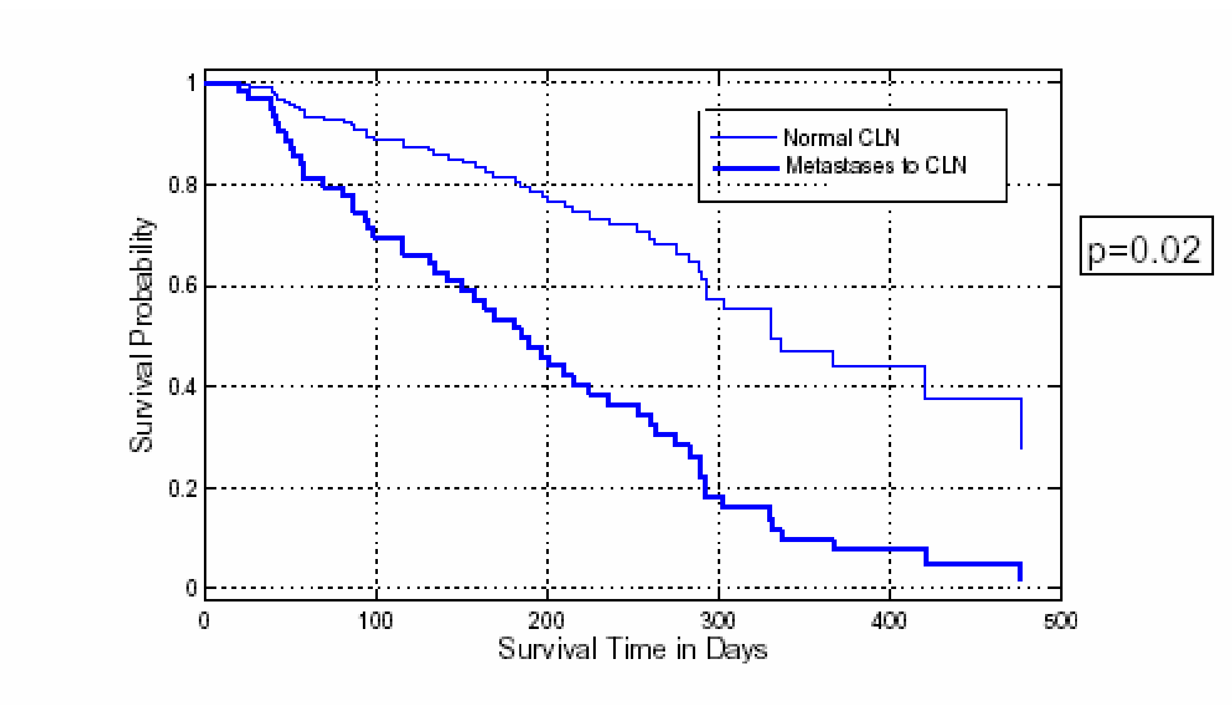
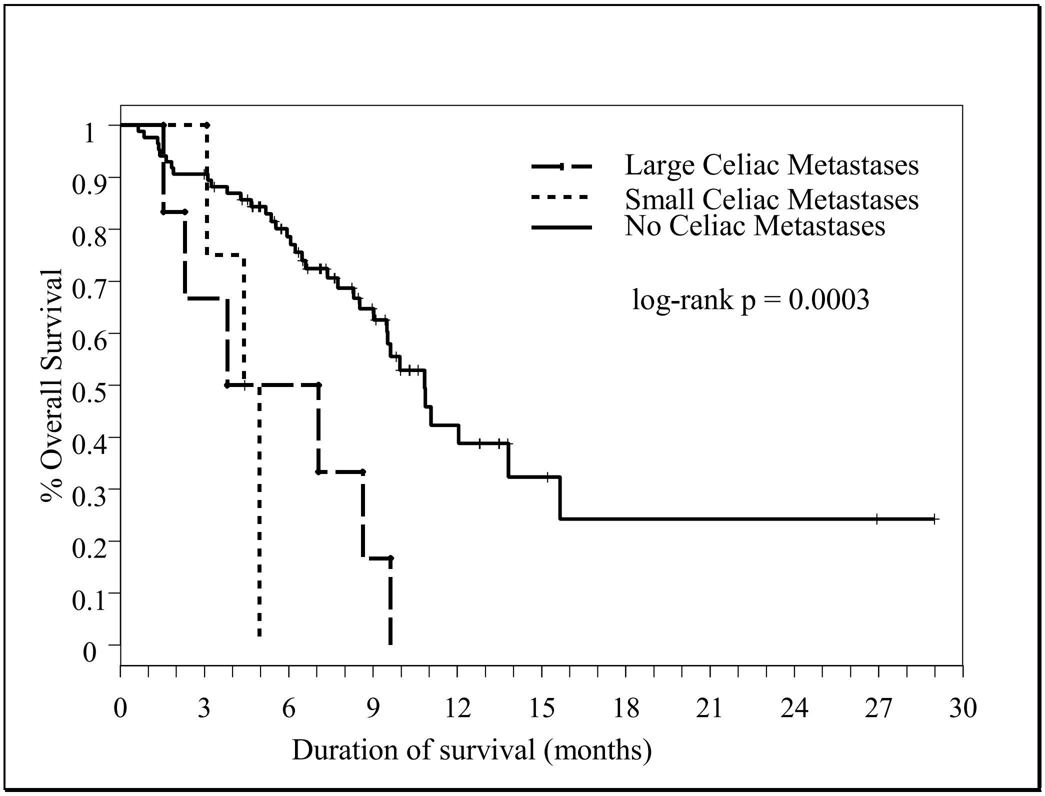


Figure 4 c.



Large Celiac Metastases
Small Celiac Metastases
No Celiac Metastases
log-rank p = 0.0003
% Overall Survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
3
6
9
12
15
18
21
24
27
30
Duration of survival (months)