Endoscopic ultrasound-guided fine needle aspiration: predictive factors of accurate diagnosis and cost-minimization analysis of on-site pathologist

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ABSTRACT

AIM: To evaluate a) new diagnoses by endoscopic ultrasound-guided real-time fine-needle aspiration (EUS-FNA) compared with EUS alone; b) the predictive factors for an accurate EUS-FNA diagnosis, and c) the cost-effectiveness of the presence of an on-site cytopathologist.

PATIENTS AND METHODS: Demographic data, ultrasonographic characteristics, technical information on EUS-FNA and cytological results were prospectively collected in 213 patients. The gold standard used was pathological examination or clinical follow-up. Operating characteristics of EUS-FNA, multivariate analysis, and a cost-minimization study of on-site evaluation were performed with these variables.

RESULTS: Samples were obtained from a total of 262 lesions: extramural masses (n = 115), lymph nodes (n = 96), cysts (n = 40) and intramural lesions (n = 11). The overall accuracy of EUS-FNA was 89% (234/262 lesions). The accuracy of EUS in discriminating between malignant and benign disease was 92% but 105 lesions (40% of the total) were classified as indeterminate. The addition of FNA to EUS allowed almost all lesions to be diagnosed with an accuracy of 90%. The only variable independently associated with an incorrect diagnosis was intramural location of the target lesion. The effectiveness of EUS-FNA in the complete series progressively increased, reaching a plateau in the fourth pass. The presence of an attendant cytopathologist was cost-effective.

CONCLUSIONS: EUS-FNA allows diagnosis of most lesions classified as indeterminate by EUS alone. The only factor independently associated with low accuracy is intramural location of the lesion. The availability of an on-site cytopathologist is cost-effective.

CONCLUSIONS: La PAAF-EE permite establecer el diagnóstico en la mayor parte de las lesiones clasificadas como indeterminadas por la EE, aplicada de manera aislada. La localización intramural de la lesión es el único factor asociado de manera independiente a una precisión diagnóstica baja. La presencia del citopatólogo durante el procedimiento es económicamente rentable.

INTRODUCTION

Endoscopic ultrasound (EUS) has largely been demonstrated to be a highly accurate technique for locoregional gastrointestinal cancer staging as well as for evaluation of large gastric folds and pancreatobiliary disturbances. The addition of EUS-guided real-time fine-needle aspiration (EUS-FNA) has improved the performance characteristics of EUS alone, although, surprisingly, few studies have prospectively and blindly compared EUS and EUS-FNA in large series of homogeneously studied lesions. For example, this kind of study has been performed in esophageal and rectal cancer but with different results. In the present large series of patients homogeneously studied by EUS and EUS-FNA, we aimed to assess what EUS-FNA adds to the diagnosis of lesions that cannot be classified as benign or malignant by EUS alone.

Some strategies, such as increasing the number of passes or having an attendant cytopathologist, have been demonstrated to be useful in improving the diagnostic yield of EUS-FNA. The type of lesion and its location (lymph node, pancreatic or other extramural masses, or intramural lesion) could also be related to the accuracy of the technique. However, the predictive factors of an accurate EUS-FNA diagnosis are still unknown.

Several studies have demonstrated that EUS-FNA is a cost-effective approach for the operative staging of esophageal carcinoma, pancreatic tumors, and rectal cancer but the cost-effectiveness of having an on-site cytopathologist has not yet been evaluated. The present study aimed to investigate: a) the clinical impact of EUS-FNA in terms of new diagnoses with respect to EUS alone in relation to the type and location of the lesion; b) the independent predictive factors for an accurate EUS-FNA diagnosis; and c) the cost-effectiveness of an on-site cytopathologist.

PATIENTS AND METHODS

Patients

Between January 2002 and February 2004, all consecutive patients referred to our unit for EUS-FNA were prospectively evaluated following the protocol described below. Patients were referred for EUS FNA of mediastinal, perigastric, periduodenal or perirectal lesions of unknown origin or for staging of gastrointestinal or pulmonary malignancies. The study was approved by the ethical research committee of Hospital Clinic and a written informed consent was obtained from all patients.

Methods

Technique

EUS-FNA was performed under conscious sedation by two fully trained endoscopists (AG, MP). Prophylactic antibiotics were administered in patients with cystic lesions as well as for endoscopic prophylaxis when appropriate. Evaluation of the target lesion and tumoral staging was initially performed with a radial mecanized echoendoscope (GF UM160 and GF UM150, Olympus Europe, Hamburg, Germany). EUS-FNA was then carried out by using a curved linear array echoendoscope (GF UMC30P, Olympus Europe) with Doppler capability and a scanning probe in the long axis of the instrument. EUS and EUS-FNA were performed following previously described standards.

Cytological material was considered adequate if the attendant cytopathologist reported that there were malignant cells or a sufficient number of representative cells for diagnosis. In putative cytological benign lesions, the decision to cease making needle passes was established by taking into account meaningful clinical factors such as the degree of clinical suspicion for underlying malignancy, the clinical impact of a non-diagnostic aspirate, cytological appearance of the aspirated material, and the total number of passes. More than one lesion could be targetted by EUS-FNA in the same patient.

The final diagnosis was made after reviewing all the material in the laboratory.

Definitions

For analysis purposes, EUS without FNA diagnosis was categorized into malignant or benign. Lesions that could not be classified into either of these two categories were considered as indeterminate. Cytological diagnoses were classified as benign, malignant, or indeterminate if only atypical cells were found or the sample was inadequate. Subsamples samples were considered malignant.

Pathological examination of resected specimens or clinical follow-up of patients not undergoing surgery were used as gold standard. In the latter group, lesions were considered malignant if there was clinical progression of the disease or response to chemotherapy or radiation therapy. Lesions were considered benign when spontaneous resolution or lack of progression was observed on imaging studies after a minimum follow-up of 12 months. In pancreatic cysts, it is now well known that mucinous cystadenomas and intraductal mucinous papillary tumors are pre-malignant lesions that should be treated surgically. For this reason, the clinical criterion was considered the most important, and these lesions were considered malignant.

Variables recorded

The following variables were recorded from each procedure according to the standard protocol for EUS in our unit and were collected in a database: demographic variables (gender, age), variables related to the lesion such as location (pancreas, mediastinum, other), type of lesion (lymph node, extramural or intramural mass, cyst) and size, EUS diagnoses (malignant, benign or indeterminate), variables related to EUS-FNA such as approach (transesophageal, transgastric, transduodenal or transrectal), the number of passes needed to reach a cytological diagnosis, and EUS-FNA diagnosis (benign, malignant or non-diagnostic).

To ensure blindness to the results of EUS-FNA, the EUS diagnosis was made before any information on cytologic assessment was registered.

Statistical analysis

Operating characteristics of EUS FNA. Accuracy, sensitivity, specificity, and positive and negative predictive values of cytological EUS-FNA were calculated with respect to the gold standard. Calculations were performed for the whole series and for each type of lesion (lymph node, extramural mass, intramural lesion and cyst). In addition to establish the accuracy of EUS-FNA in the clinical setting, this parameter was also calculated by considering inadequate samples as misdiagnosed.

Clinical impact of EUS-FNA in terms of new definitive diagnoses. The clinical impact of EUS-FNA in terms of new definitive diagnoses was calculated by comparing the percentage of lesions diagnosed by EUS-FNA and its performance characteristics with the same figures for EUS alone. The calculations were made for the whole series and for each specific type of lesion.
Predictive factors for an accurate EUS-FNA diagnosis. Evaluation of the factors influencing the results of EUS-FNA was performed for the whole series and for each type of lesion using all the above-mentioned variables. Comparisons between qualitative variables were performed by the χ² test, with application of Yates’ correction when needed. Continuous variables were expressed as mean ± standard deviation and analyzed by Student’s t-test. A stepwise logistic regression model was used to assess the independent predictive factors for correct diagnosis. A p-value of less than 0.05 was considered statistically significant.

Accuracy of EUS-FNA according to the number of passes. To establish the effectiveness of the presence of a cytopathologist during EUS-FNA, the results achieved in the presence of a pathologist were compared with those that theoretically would have been obtained if a particular number of passes had been performed without on-site evaluation. For this calculation, accuracy was determined after each particular number of passes, assuming that when a lesion was actually diagnosed in a specific pass, any additional subsequent pass would produce an identical result. This analysis was performed for the whole series and for each type of lesion. The relationship between the type of lesion and the number of passes was analyzed by analysis of variance (ANOVA) procedures using the F test statistic.

Cost-minimization analysis of on-site evaluation. The outcome measure for the cost-minimization analysis was correct diagnosis. Costs included the salaries of the endoscopist, pathologist, anesthesiologist, nurse and technician, as well as sedation and material for conventional cytology. Physician, nurse and technician fees were calculated assuming a 1-year full salary of 47,000 USD, 30,000 USD and 18,000 USD, respectively, according to Spanish national health system rates, and an average time for obtaining the specimen and performing on-site examination of 15 min per sample. The general costs of EUS imaging and FNA procedures (material, overnight admission, etc.) were not considered since they were identical to that for other types of lesion (lymph node, 91% [CI, 85-95]). Both false-positive results occurred in lymph nodes (96% [CI, 91-97]) and in 2 of the 57 benign lesions (specificity, 90%; CI, 94-98). Both false-positive results occurred in pancreatic lesions. One corresponded to a patient with a pancreatic tumor diagnosed by helical CT in whom EUS findings were not conclusive for malignancy but those of EUS-FNA were consistent with adenocarcinoma. The pathologic diagnosis after surgery was focal «non-specific» pancreatitis. Three years later the patient is alive and has no signs of pancreatic cancer. The other false-positive result occurred in a patient with a pancreatic cyst in which EUS-FNA was consistent with mucinous cystoadenoma whereas the surgical specimen showed a serous cystoadenoma. There were no false-positive results in lymph nodes or intramural lesions (specificity, 100%). The sensitivity of EUS-FNA for the diagnosis of malignancy in each different type of lesion was as follows: 89% for lymph nodes (CI, 83-95), 95% for extramural tumors (CI, 91-99), 67% for intramural lesions (CI, 26-100) and 100% for cysts; therefore, diagnosis was correct in 250 of the 262 lesions evaluated (accuracy 94%; CI, 91-97). To establish the overall performance characteristics of EUS-FNA in a clinical setting, the analysis was repeated considering inadequate samples as misdiagnosed. The overall accuracy of EUS-FNA was 89% (CI, 85-93) (234/262 lesions). When this figure was calculated for each specific type of lesion, the overall accuracy for intramural lesions (45%; CI, 16-74) was much lower than that for other types of lesion (lymph node, 91% [CI, 85-97]; masses, 91% [CI, 86-96], and cysts, 92% [CI, 83-100]) (table II).

### RESULTS

A total of 213 consecutive patients underwent EUS-FNA. According to the definitive diagnosis, lesions were benign in 54 (25%) patients and malignant in 159 (75%). The definitive diagnosis was established by clinical follow-up in 137 patients (64%) and by surgical specimen in the remaining 76 (36%). Demographic characteristics and the number and characteristics of the 262 targeted lesions are detailed in Table I. A total of 551 samples were obtained from these lesions, representing 2.1 ± 1.1 passes per sample, respectively. The number of samples required to achieve a correct diagnosis was multiplied by these costs.

### Operating characteristics of EUS-FNA

Adequate cytological specimens were obtained in 250 of the 262 lesions (95%). In lesions in which the material was adequate for diagnosis, EUS-FNA revealed malignancy in 179 of the 193 malignant lesions (sensitivity, 93%; CI, 90-96) and in 2 of the 57 benign lesions (specificity, 96%; CI, 94-98). Both false-positive results occurred in pancreatic lesions. One corresponded to a patient with a pancreatic tumor diagnosed by helical CT in whom EUS findings were not conclusive for malignancy but those of EUS-FNA were consistent with adenocarcinoma. The pathologic diagnosis after surgery was focal «non-specific» pancreatitis. Three years later the patient is alive and has no signs of pancreatic cancer. The other false-positive result occurred in a patient with a pancreatic cyst in which EUS-FNA was consistent with mucinous cystoadenoma whereas the surgical specimen showed a serous cystoadenoma. There were no false-positive results in lymph nodes or intramural lesions (specificity, 100%). The sensitivity of EUS-FNA for the diagnosis of malignancy in each different type of lesion was as follows: 89% for lymph nodes (CI, 83-95), 95% for extramural tumors (CI, 91-99), 67% for intramural lesions (CI, 26-100) and 100% for cysts; therefore, diagnosis was correct in 250 of the 262 lesions evaluated (accuracy 94%; CI, 91-97). To establish the actual performance characteristics of EUS-FNA in a clinical setting, the analysis was repeated considering inadequate samples as misdiagnosed. The overall accuracy of EUS-FNA was 89% (CI, 85-93) (234/262 lesions). When this figure was calculated for each specific type of lesion, the overall accuracy for intramural lesions (45%; CI, 16-74) was much lower than that for other types of lesion (lymph node, 91% [CI, 85-97]; masses, 91% [CI, 86-96], and cysts, 92% [CI, 83-100]) (table II).
EUS alone was able to discriminate between malignant and benign disease in 60% of lesions with 92% accuracy. The remaining 105 lesions (40% of the total) were classified as indeterminate. The addition of FNA to EUS allowed diagnosis of almost all lesions (89%) with an accuracy of 90%.

As shown in table III, the addition of FNA in lymph nodes increased the number of lesions with a definitive diagnosis (from 29 to 95) but did not increase accuracy (90% vs 92%). For cysts, the addition of FNA doubled sensitivity in the detection of malignancy (50% vs 100%). Importantly, for lymph nodes and intramural lesions, the addition of FNA produced no false-positive or false-negative results in the subgroup of patients with a correct EUS diagnosis. However, FNA led to a mistaken diagnosis of benign disease in 3 of the 87 malignant extramural lesions with a correct diagnosis by EUS alone, the three lesions being pancreatic cancers.

Predictive factors of accurate diagnosis
Among the analyzed variables (Table I), the only factors associated with a correct diagnosis by EUS-FNA were the type and diameter of the lesion (p < 0.05). Lesions located in the gastrointestinal wall or those with a larger diameter were associated with a higher proportion of incorrect diagnoses than the remaining lesions. After the multivariate analysis, the only variable independently associated with an incorrect diagnosis was intramural location of the target lesion.

Accuracy of EUS-FNA according to the number of passes
The overall accuracy of EUS-FNA was calculated after a particular number of passes (Fig. 1). The effectiveness of EUS-FNA in the whole series progressively increased from 36% to 89%, reaching a plateau in the fourth pass. This curve was similar for extramural masses, lymph nodes and cysts but the plateau appeared in the third pass in lymph nodes and cysts. The accuracy of EUS-FNA for intramural lesions increased from 0.9% to 45% and reached a plateau in the fourth pass.

### TABLE II. Performance characteristics of EUS-FNA*

<table>
<thead>
<tr>
<th>All lesions</th>
<th>Accuracy</th>
</tr>
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<tbody>
<tr>
<td>Whole series</td>
<td>262</td>
</tr>
<tr>
<td>Lymph node</td>
<td>96</td>
</tr>
<tr>
<td>Extramural masses</td>
<td>115</td>
</tr>
<tr>
<td>Intramural lesions</td>
<td>11</td>
</tr>
<tr>
<td>Cyst</td>
<td>40</td>
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</tbody>
</table>

* Inadequate samples are considered as misdiagnosed.

### TABLE III. Clinical Impact of EUS-FNA with respect to EUS alone

<table>
<thead>
<tr>
<th>N*</th>
<th>Acc</th>
<th>Sn</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole series (n = 262)</td>
<td>EUS</td>
<td>157</td>
<td>92</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>250</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>Lymph nodes (n = 96)</td>
<td>EUS</td>
<td>29</td>
<td>90</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>95</td>
<td>92</td>
<td>89</td>
</tr>
<tr>
<td>Extramural masses (n = 115)</td>
<td>EUS</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>111</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>Intramural lesions (n = 11)</td>
<td>EUS</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>6</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>Cysts (n = 40)</td>
<td>EUS</td>
<td>29</td>
<td>79</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>38</td>
<td>97</td>
<td>100</td>
</tr>
</tbody>
</table>

N*: lesions that could be classified as benign or malignant by EUS or lesions in which adequate material was obtained by EUS-FNA.

ACC: accuracy; EUS: endoscopy ultrasound; FNA: fine-needle aspiration; Sn: sensitivity; Sp: specificity.
is feasible from EUS-FNA samples but is limited to wide
ed that immunohistochemical analysis (c-KIT and Ki-67)
our series, 8 of the 11 intramural lesions were submucos-
bles the reason why an on-site cytopathologist was not
results of the multivariate analysis showed that intramural
lesions to confirm or preclude malignancy before any
treatment is decided
malignancies adjacent to the gastrointestinal wall but is
less efficient for the diagnosis of intramural lesions. Ac-
cording to our results, the efficacy of EUS-FNA mainly
depends on the location of the lesion. Indeed, EUS-FNA
is a highly specific and sensitive technique for the diag-
nosis of lesions located in the posterior mediastinum and
the pancreatic, perirectal and perigastric areas. However,
the overall accuracy of this technique in the diagnosis of
intramural lesions, especially when inadequate samples
are considered as misdiagnosed, is much lower. The re-
sults of the multivariate analysis showed that intramural
location was the only independent factor related to low
accuracy of EUS-FNA and this location was also proba-
bly the reason why an on-site cytopathologist was not
cost-effective in this group of lesions. Nevertheless, in
our series, 8 of the 11 intramural lesions were submucos-
al tumors, in which obtaining adequate material for cyto-
logical diagnosis appears to be more difficult. Moreover,
even with an adequate sample, the possibility of estab-
lishing a diagnosis of malignancy or benign disease by
cytology alone is low, since diagnosis is based on mitotic
count and tumoral size. Ando et al recently demonstrat-
ed that immunohistochemical analysis (c-KIT and Ki-67)
is feasible from EUS-FNA samples but is limited to wide
samples of adequate material. Therefore, the use of larger
diameter needles or trucut devices could be an alternative
approach for the diagnosis of intramural lesions through
immunohistochemical analysis.
The clinical impact of EUS-FNA in patients with malig-
nancies of the gastrointestinal tract has previously been studied. However, there is little information on the
role of EUS-FNA versus EUS alone in the diagnosis of
malignancy according to the type and location of the le-
sion in large series of patients homogeneously studied
with both techniques. As a whole, EUS was able to clas-
sify only 60% of the lesions whereas the addition of FNA
allowed the majority of the lesions to be diagnosed with-
out decreasing accuracy. The impact of EUS-FNA is ob-
vious in lymph nodes. EUS-based criteria for malignant
lymph nodes are highly specific but only 25% of these
nodes present these features. For this reason, and be-
cause cytopathological diagnosis is crucial for therapeutic
decision making and prognosis, EUS-FNA is of prime im-
portance in a high percentage of oncological patients with
lymph node lesions. The clinical impact of EUS-FNA in
patients with pancreatic masses who are candidates for
surgery is less important since a cytological result nega-
tive for malignancy does not usually change the manage-
ment. In contrast, EUS-FNA is mandatory in non-surgical
lesions to confirm or preclude malignancy before any
treatment is decided. Finally, the impact of EUS-FNA
in cystic lesions has not been specifically evaluated.
However, we demonstrate that the addition of FNA in-
creases the sensitivity of EUS in the diagnosis of malig-
nancy from 50 to 100% and allows diagnosis of 100% of
cysts classified as indeterminate by EUS alone.

The most important predictive factor for obtaining an ad-
equate sample for pathological diagnosis is the number of
passes performed. However, the availability of an on-site
cytopathologist may greatly influence this parameter.
Klapman et al have recently analyzed the importance of
having an attendant cytopathologist. This study compared
the EUS-FNA cytological results obtained by the same
endosonographer in a center with an on-site cytopatholo-
gist and in another center without a cytopathologist. The
chances of obtaining a diagnosis at the former were ap-
proximately twice those at the latter. However in the cen-
ter where the cytopathologist was not in the operating
room, the low number of passes performed (from 2 to 3
passes in pancreatic lesions) could have biased the re-
sults. Erickson et al analyzed the number of needle passes
required to diagnose pancreatic malignancies using EUS-
FNA and concluded that without a cytopathologist in at-
tendance, the low number of passes performed (from 2
to 5 passes should be made for pancreatic masses and 2 to 3
for liver or node metastasis). In our se-
ries, the accuracy of EUS-FNA was directly related to the
number of passes performed. Accuracy progressively in-
creased with the number of passes but reached a steady
value at the third or fourth pass, depending on the type of
lesion. These findings suggest that if an attendant pathol-
ologist is not available, the number of passes performed
should be at least 3 to 4, depending on the type of lesion.
However, data in the literature indicate a higher number
of passes are required to obtain such results and conse-

<table>
<thead>
<tr>
<th>Attendant cytopathologist</th>
<th>Overall accuracy</th>
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<tbody>
<tr>
<td>With</td>
<td>234/262</td>
</tr>
<tr>
<td>Without</td>
<td>233/262</td>
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</table>

**Cost-minimization analysis of on-site evaluation**

To establish the cost-effectiveness of the presence of an
attendant cytopathologist, the results obtained with this
strategy were compared with those that would have been
obtained with a particular number of passes without on-
site examination (table IV). The overall accuracy obtained
with 4 passes (87%) was similar to that obtained under
pathologist guidance (89%) with a mean of 2.1 passes per
lesion. Considering 20 US$ per pass with an attendant
pathologist and 11 US$ per pass without the attendant
costs per correct diagnosis x total cost of the strategy / number of patients in
whom a correct diagnosis was achieved.

<table>
<thead>
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<tbody>
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<td>Without</td>
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</tr>
</tbody>
</table>

**Cost-per-pass analysis**

Cost per correct diagnosis = total cost of the strategy / number of patients in
whom a correct diagnosis was achieved.
quenty certain factors related to the patient, clinical as-
pects or the lesion may influence the decision on how
many biopsies to perform.

The cost-effectiveness of an attendant cytopathologist has
not previously been analyzed. Prior data from percuta-
nous FNA suggest that on-site evaluation is cost-effec-
tive because it avoids repeating FNA procedures due to
non-diagnostic samples\(^6\). Our results demonstrate that an
attending cytopathologist can minimize the number of
passes required for diagnosis and that this strategy is cost-
effective.

This study presents certain limitations. Firstly, there was
no control group with respect to the availability of an at-
tending cytopathologist. Nevertheless, since the lesions
were systematically sampled until adequate material was
obtained, the results that would have been obtained with
the same number of passes in the absence of an attendant
pathologist can be inferred. Secondly, the final diagnosis
depended on surgical pathology in only 36% of patients.
However, most of the patients that lacked a surgical spec-
imen had pancreatic cancer, in which short survival al-
lowed us to confirm the diagnosis. Thirdly, cost-effect-
tiveness analysis can show noteworthy deviations depend-
ing on the country and health system considered, mainly
due to differences in salaries. Accordingly, ex-
trapolation of our results to other centers or medical orga-
nizations would require these figures to be recalculated.

In conclusion, this study demonstrates that EUS-FNA al-
lows diagnosis of most lesions classified as indeterminate
with low accuracy is intramural location of the lesion.

The availability of an attendant pathologist seems to in-
crease the diagnostic yield of FNA, minimizes the num-
ber of passes and is a cost-effective strategy.

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