

REVIEWS

Role of endoscopic ultrasonography with and without fine needle aspiration cytology in the diagnosis and staging of lymphoma

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Abstract

Diagnosis of lymphoma is frequently challenging. The complexity of the sub-classification of lymphomas along with the necessity of a high quality sample leads to costly and invasive procedures in order to achieve the correct diagnosis. Endoscopic ultrasound is a valuable tool for the diagnosis and staging of gastrointestinal neoplasms as well as those that involve structures in the vicinity of the digestive tract. Whereas most gastrointestinal lymphomas are diagnosed and sub-classified using endoscopic biopsies, those involving deep-seated organs or lymph nodes might be targeted by minimal invasive procedures as endoscopic ultrasound-guided fine needle aspiration cytology. Endoscopic ultrasound is also an accurate tool for the local staging of gastrointestinal lymphomas and prediction of the response to *Helicobacter pylori* eradication. This review summarizes the indications and evidence of endoscopic ultrasonography with or without fine needle aspiration cytology in the diagnosis and staging of lymphoma.

Key words

Endoscopic ultrasonography, Lymphoma, Fine needle aspiration cytology

1 Introduction

Diagnosis of lymphoma is a clinical challenge. Whereas the diagnosis of gastrointestinal lymphomas is straight forward by taking multiple endoscopic biopsies^[1], the diagnosis of deep-seated nodal or primary organ lymphoma is often difficult or risky if percutaneous imaging techniques such as ultrasound (U.S.) or computed tomography (CT) are used^[2,3]. In fact, most of them are diagnosed using invasive and expensive procedures such as thoracotomy, laparotomy, laparoscopy or mediastinoscopy. In addition, lymphoma classification has increased its complexity in recent years with the development of molecular and immunohistochemical techniques. The recent classification of the World Health Organization (WHO)^[4] provides 70 different forms of lymphoma. An accurate diagnosis and classification is critical as prognosis and treatment of lymphomas change depending on the stage of disease and histopathological classification. In order to achieve this goal, high quality samples are usually required^[5,6].

Gastrointestinal lymphomas are the most frequent primary extranodal lymphomas. Endoscopic ultrasound (EUS) is a technique that combines conventional endoscopic and ultrasound image. The proximity of the ultrasound transducer to the gastrointestinal wall and neighboring organs makes it an ideal tool for staging gastrointestinal wall lesions, and evaluation of deep-seated abdominal nodes or organs inaccessible by other techniques. In addition, EUS allows fine needle aspiration cytology (EUS-FNA) or biopsy (EUS-B) providing cytological or histological samples of good quality for the diagnosis of different types of lesions ^[7, 8]. Ancillary techniques such as flow cytometry (FC) or immunohistochemistry can be performed on EUS-FNA samples improving diagnostic yield ^[9]. EUS has several advantages over other imaging techniques such as real-time sampling, low risk of complications because of its proximity to the gastrointestinal wall (i.e. perforation, bleeding and seeding) and sampling of small lesions ^[10].

This review focuses on the applications of EUS in extranodal lymphomas (gastrointestinal, pancreatic and splenic) as well as in nodal lymphoma.

2 Primary extranodal lymphomas

Primary extranodal lymphomas constitute 25-35% of the non-Hodgkin lymphoma (NHL) ^[11, 12]. The digestive tract is the most common site (35-50%) of the primary extranodal lymphoma ^[13, 14]. In primary lymphomas of the digestive tract 60% of cases involve the stomach.

2.1 Gastrointestinal lymphomas

Gastrointestinal lymphomas constitute the majority of extranodal lymphomas. Overall, primary gastric lymphomas constitute 70%, followed by small bowel, colon and rectal lymphomas ^[15], MALT lymphoma (mucosa-associated lymphoid tissue) and diffuse large B cell lymphoma (DLBCL) are the most frequent. Other lymphomas such as mantle lymphomas, follicular lymphomas or peripheral T-cell lymphomas are more rarely found. The diagnosis and classification of gastrointestinal lymphomas are usually achieved by large endoscopic biopsies (jumbo biopsies, snare biopsies or biopsies within biopsies). Once diagnosed and classified, the next step is staging the tumor. EUS is the best imaging technique to assess the gastrointestinal wall. It makes possible to distinguish the different layers and it is considered the technique of choice for staging of esophageal or gastric tumors ^[16]. Although EUS is able to stage the tumor infiltration in DLBCL, it has a low impact in this tumor as it does not really change the clinical management.

Unlike DLBCL, EUS is particularly useful in the evaluation of MALT lymphoma ^[17]. Over 90% of MALT lymphomas are associated with *Helicobacter pylori* infection and several studies show that in early stages (mucosal or submucosal involvement), the disease heals after treatment ^[18-20]. On the other hand, in advanced stages the treatment of choice is chemotherapy or immunotherapy. EUS imaging is not specific of MALT lymphoma and therefore it has no diagnostic value. However, EUS is extremely accurate in differentiating early invasion (T1 mucosal or submucosal, EI1 of Ann Arbor classification) from T2-T4 (EI2) or TxN1 (EII1) ^[21]. Diagnostic accuracy for T staging has ranged between 80% and 90% across the studies ^[22, 23], whereas for N stage, it ranges between 71% and 90% ^[22, 24]. Accuracy is even higher when EUS is associated with FNA and FC being reported as high as 97% ^[25]. Another indication is the prognostic value of EUS. Tumoral infiltration assessed by EUS correlates with tumoral healing after *Helicobacter pylori* treatment, so, it is not surprising the great EUS value for predicting response to therapy. Thus, different studies agree that when wall involvement assessed by EUS is superficial (mucosal or submucosal), the chance of healing after eradication therapy is more than 75% ^[18, 26, 27].

Some authors found a high correlation between histological improvement and normalization of the gastric wall evaluated by endoscopic ultrasound ^[17, 28, 29], supporting its usefulness in surveillance after treatment. However, in other reports that correlation was much lower ranging from 33% and 54% ^[30, 31]. Therefore, at present, EUS cannot be recommended for MALT lymphoma surveillance after treatment, and biopsies remain the only reliable proof of residual disease. Finally, EUS-FNA makes sampling possible of either regional lymph nodes or in the rare cases with thickened gastric folds in

which endoscopic biopsy results negative for malignancy [32]. The use of large FNA needles (19 gauge) provides histological samples, useful for ancillary techniques such as immunohistochemistry or FC [33].

2.2 Pancreatic lymphoma

Less than 0.5% of pancreatic tumors are primary pancreatic lymphomas (PPL) [15]. Although almost 30% of non-Hodgkin lymphomas involve the pancreatic gland, less than 1% are considered PPL [34]. However, despite its rarity, to achieve a correct diagnosis of this disease is crucial as the prognosis and the management of PPL compared with the much more frequent pancreatic adenocarcinoma is completely different. The diagnostic criteria for PPL include [35]: 1) mass which predominantly affects the pancreas, 2) peripancreatic node involvement, 3) absence of palpable lymph nodes, 4) absence of mediastinal involvement, 5) absence of hepatosplenic dissemination, 6) blood cell differential count normal.

The diagnosis of this disease is challenging. EUS is an ideal technique to evaluate the pancreatic gland because of the proximity of the gastric wall and duodenum and safety. EUS pattern has been described as a “strongly hypoechogenic appearance in the pancreas, hypertrophy in all its segments, a hyperechoic wall in the common pancreatic duct and multiple isoechoic pancreatic nodes” [36, 37]. However, this pattern is not specific enough to differentiate PPL from other solid pancreatic masses. When suspected, a cytological or histological sample is needed in order to prescribe a proper treatment [9]. Only one study evaluated the diagnostic utility of EUS-FNA in the diagnosis of PPL [2]. This case series included 14 patients with final diagnosis of PPL who underwent EUS-FNA. The authors evaluated the diagnostic yield of cytology alone versus the combination of cytology and FC. The final diagnosis of lymphoma was improved from 30.8% to 84.6% when the combination of techniques was used. Furthermore, the FC sub-classification of lymphoma was possible in all the diagnosed cases. Several case reports using EUS-FNA for PPL have also been published [36, 37].

2.3 Splenic lymphoma

Lymphoma is one of the most common causes of splenic focal masses. Other lesions include metastases, tuberculosis, sarcoidosis, abscesses or infarction [38]. Although these lesions can be diagnosed by percutaneous biopsy, it may increase the risk of complications, because the spleen is surrounded by structures such as lung, left kidney and colon. A multicenter Italian study evaluated the efficacy and safety of percutaneous puncture of splenic injuries in 398 patients [3]. Lymphoma was the most frequent diagnosis and the diagnostic accuracy by cytology and histology was similar (88.4% and 88.3% respectively). It is worth pointing out that the incidence of major complications was 5.3%, which included hemoperitoneum, pneumothorax, subcapsular hematoma and subacute hemorrhage.

Table 1. EUS-FNA in splenic lymphoma

Author	Patients (n)	Design	Needle size	Technique	Yield n, (%)	Sub-typing yield n, (%)	Pasesst†
Fritscher-Ravens, et al	12 (3)	Prospective	22 G	Cytology	2/3 (66.6)	2/3 (66.6)	2 (1-4)
Eloubeidi, et al	6 (3)	Prospective	22 G	Cytology Flow citometry	2/3 (66.6)	2/3 (66.6)	4 (4-5)
Iwashita, et al	5 (2)	Prospective	19 G	Cytology Flow Citometry Cytogenetic analysis Immunohistochemistry	2/2 (100)	2/2 (100)	2 (2-3)

† Median and range

Three case series have evaluated the usefulness of EUS-FNA in focal splenic lesions including a total of 23 patients (Table 1) [38-40]. The diagnosis of lymphoma was correctly established in 75% of cases. In addition, sub-classification was possible in all of them. There were no major complications.

3 Nodal lymphomas

Histological evaluation is the gold standard for final diagnosis of lymphoma^[4], whereas the value of cytology is controversial. Some authors claim that the use of cytologic examination combined with FC could obviate more invasive procedures for the study of this disease^[41-43]. Cytology combined with FC is especially useful at differentiating reactive B from monoclonal B cell neoplasms and therefore in many centers these techniques are used as the initial study for suspected nodal lymphoma^[44]. Several studies demonstrate the efficacy of cytology in the diagnosis of nodal lymphomas. In the studies using a percutaneous approach, sensitivity and diagnostic accuracy ranged from 66%-90% and 80%-60% respectively^[45-47]. FC may also be helpful in the immunological sub-typing of nodal lymphoma. Several studies have used EUS-FNA in combination with the FC for the diagnosis of nodal lymphoma (Table 2); all of them with a retrospective design^[32, 42, 48-52]. FC significantly increased sensitivity (72.7% to 100%) and specificity (93% to 100%) for the diagnosis of lymphoma compare with the cytomorphic assessment alone (sensitivity and specificity of 30.8% to 87% and 0% to 100%, respectively). Limitations of FC include the difficulties in the diagnosis of T cell lymphomas because they express some markers typically found in mature T lymphocytes and Hodgkin lymphoma, due to the rarity of the Reed-Steinberg cells in cytology specimens and the absence of monoclonality^[53, 54]. Obtaining histological samples by EUS can solve these problems. Currently, large-caliber FNA needles (19 gauge) are available. These needles provide a larger sample adequate for histological analysis. This issue has been evaluated in several studies, in which histological specimens obtained by EUS were used for immunological sub-typing of lymphoma^[33, 39, 55-57]. Overall, 240 patients were included in these studies. In general, a large FNA needle was used (Quick Core™ needle. Cook Endoscopy, Winston Salem, NC. Or 19 gauge needle cytology) and cytomorphic assessment as well as ancillary techniques (FC and immunohistochemistry) were performed. The diagnosis of lymphoma was achieved in 94% of the cases and sub-typing according to WHO classification in 85%. Yasuda, et al.,^[54] reported a success rate of 85.7% in the grading of follicular centre cell lymphoma. In 29 cases sub-classification was not possible. False-negative results were attributed to significant tumor necrosis^[56], insufficient sample^[57], and technical limitations related to the type of needle or needle size (Quick Core™ needle. Cook Endoscopy Inc, Limerick, Ireland)^[56].

Table 2. Diagnostic Yield of EUS-FNA with or without ancillary techniques

Author (yr)	Patients or lesions N (N- lymphomas)	Design	Needle type	Passes (median)	Cytology Yield (%)	Cytology and ancillary techniques yield (%)
Ribeiro, et al.*	38 (23)	Retrospective	22 G	NR**	S= 44 E=90	S=74 E=93
Stelow, et al.*‡	12 (8)	Retrospective	21/25 G	2.2±2.4	S=50 E=100	S=87.5 E=100
Mehra, et al.*	31 (11)	Retrospective	22 G	3 (1-7)	NR	S=72.7 E=100
Pugh, et al.*†	385 (13)	Retrospective	22 G	NR	NR	S=92.3 E=100
Al-Haddad, et al.*	54 (38)	Retrospective	22 G	4.9 (1-13)	S=87 E=50	S=87 E=93
Miletic, et al.*	16 (7)	Retrospective	22 G	NR	S=100 E=88.8	S=100 E=100
Stacchini, et al.*†	56 (11)	Retrospective	19/22/25 G	4.5 (3-6)	NR	S=100 E=100

* Use of Flow cytometry as ancillary technique

** Not reported

† Use of immunocytochemistry

‡ Use of cytogenetic analysis

Only 7 complications were reported (2.9%): 3 cases of submucosal hematoma, 1 case of mild abdominal pain, 2 cases of fever after the procedure. (39, 55-57) One patient with cirrhosis died from variceal bleeding, probably not related to the procedure^[56].

Another useful technique in this setting is the assessment of cytogenetic abnormalities. Several lymphomas have characteristic genetic abnormalities with a prognostic value and can be helpful in the differential diagnosis. They include specific chromosomal translocations in: follicular lymphoma, mantle cell lymphoma, anaplastic large cell lymphoma, Burkitt lymphoma, and MALT. A recent study, using percutaneous FNA assessed the sensitivity of fluorescence in situ hybridization (FISH) in lymphoma sub-typing^[58]. FISH was successful in 95.3% of the cases and sub-typing was possible in 61.6%. Moreover, this technique changed the final diagnosis in 10% of the cases.

Regarding EUS-FNA, karyotyping has been rarely performed^[32, 38, 47]. In the largest series^[55], 240 patients with suspected lymphoma were included. Finally, 152 were diagnosed of lymphoma. Karyotyping was assessed by conventional G-band karyotype analysis. Specific cytogenetic abnormalities were detected in 43 patients, whereas in 188, cell proliferation was insufficient during cell culture. Sensitivity for cytogenetic analysis was only 13.8%. The authors suggested FISH as an alternative procedure in order to improve the sensitivity of cytogenetic assessment.

4 Conclusion

Endoscopic ultrasound is a useful tool for locoregional staging of MALT lymphoma, as well as a good predictor of response to eradication therapy. In addition, EUS-FNA is a useful technique in patients with suspected lymphoma located in organs whose puncture by other techniques is difficult because of their access or it can be of a high risk for the patient, as is the case of the pancreatic gland or spleen. Besides the technological development in this field makes it possible to obtain histological samples often complex and can avoid the use of more invasive diagnostic procedures.

Conflict of interests

The authors declare that no competing interests exist.

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