Gastroenterology Report, 2022, 1–7

https://doi.org/10.1093/gastro/goac022
Original Article

ORIGINAL ARTICLE

Diagnostic performance of endoscopic ultrasound-guided tissue acquisition of splenic lesions: systematic review with pooled analysis

Andrea Lisotti [1,*], Stefano Francesco Crinò[2], Benedetto Mangiavillano[3], Anna Cominardi[1], Andrew Ofosu[4], Nicole Brighi[5], Flavio Metelli[1], Rocco Maurizio Zagari[6], Antonio Facciorusso[2,7] and Pietro Fusaroli[1]

[1]Gastroenterology Unit, Hospital of Imola, University of Bologna, Imola, Italy, [2]Department of Medicine, Gastroenterology and Digestive Endoscopy Unit, The Pancreas Institute, University Hospital of Verona, Verona, Italy, [3]Gastrointestinal Endoscopy Unit, Humanitas—Mater Domini Castellanza, Varese, Italy, [4]Gastroenterology and Hepatology, Stanford University, Stanford, CA, USA, [5]Department of Medical Oncology, IRCSS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Medola, Italy, [6]Department of Medical and Surgical Sciences—DIMEC, University of Bologna, Bologna, Italy; [7]Department of Surgical and Medical Sciences, Section of Gastroenterology, University of Foggia, Foggia, Italy

*Corresponding author. Gastroenterology Unit, Hospital of Imola, University of Bologna, via Montericco 4, Imola, 40026, Italy. Tel: +39-(0)542-662289; Fax: +39-(0)542-662409; Email: lisotti.andrea@gmail.com

Abstract

Background Focal splenic lesions are usually incidentally discovered on radiological assessments. Although percutaneous tissue acquisition (TA) under trans-abdominal ultrasound guidance is a well-established technique for obtaining cyto-histological diagnosis of focal splenic lesions, endoscopic ultrasound (EUS)-guided TA has been described in several studies, reporting different safety and outcomes. The aim was to assess the pooled safety, adequacy, and accuracy of EUS-TA of splenic lesions.
Methods A comprehensive review of available evidence was conducted at the end of November 2021. All studies including more than five patients and reporting about the safety, adequacy, and accuracy of EUS-TA of the spleen were included.
Results Six studies (62 patients) were identified; all studies have been conducted using fine-needle aspiration (FNA) needles. Pooled specimen adequacy and accuracy of EUS-TA for spleen characterization were 92.8% [95% confidence interval (CI), 86.3%–99.3%] and 88.2% (95% CI, 79.3%–97.1%), respectively. The pooled incidence of adverse events (six studies, 62 patients) was 4.7% (95% CI, 0.4%–9.7%).
Conclusion EUS-FNA of the spleen is a safe technique with high diagnostic adequacy and accuracy. The EUS-guided approach could be considered a valid alternative to the percutaneous approach for spleen TA.

Key words: biopsy; cancer; lymphoma; metastasis; leukemia

Submitted: 12 January 2022; **Revised:** 9 March 2022; **Accepted:** 10 May 2022

Introduction

Most focal and diffuse splenic abnormalities are found incidentally, challenging clinicians in the differential diagnosis. In patients with a known malignancy or a disease that involves the spleen, the clinical presentation may include pain, signs and symptoms of infection, and associated findings on cross-sectional imaging. A history of abdominal trauma must always be investigated in order to rule out a post-traumatic etiology. Laboratory investigation can also bring important diagnostic information [1].

The differential diagnosis of focal splenic lesions includes cystic lesions, primary vascular neoplasms, infectious or inflammatory processes, lymphoproliferative disorders, and metastases. The majority of the asymptomatic patients harbor benign and clinically insignificant lesions. However, radiologic imaging does not always yield conclusive findings, especially when other clinical or laboratory clues are absent. For this reason, invasive procedures such as percutaneous image-guided biopsy are sometimes warranted. Based on literature evidence, percutaneous image-guided core needle biopsy of the spleen has sensitivity and specificity of ~87% and ~97%, respectively [2, 3]. In these patients, the benefits of an accurate diagnostic work-up must be accurately weighed against the risks of adverse events associated with the percutaneous biopsy [2–5]. In extreme conditions, splenectomy could be considered a rescue strategy for both diagnostic and therapeutic intent.

Endoscopic ultrasound (EUS)-guided tissue acquisition (TA) is a well-established technique for obtaining cyto-histological diagnosis of gastrointestinal sub-epithelial lesions, tumors located in the pancreas, liver, and lymph nodes [6–12]. EUS-guided TA of splenic lesions has also been described, but evidence is predominantly linked to small retrospective studies [13–18].

The aim of this study was to assess the safety, adequacy, and accuracy of EUS-guided TA of the splenic parenchyma and its lesions.

Material and methods

Study design and search strategy

We conducted a comprehensive systematic review of scientific articles published up to 30 April 30 2021 through MedLine using PubMed, EMBASE, Scopus, the Cochrane Central register, and Google Scholar interfaces. Key words used in search included a combination of “endoscopic ultrasound,” “spleen,” “biopsy,” and “aspiration.” The search strategy used in MedLine was based on the following search string with MeSH terms: “endoscopic ultrasound” AND “spleen” OR “splenic” AND “biopsy” OR “aspiration.” Additionally, the bibliography of retrieved articles and reviews was manually analysed to find other additional eligible studies that eluded the primary search. The search was restricted to studies on human adults, published in the English language.

Selection criteria

Two authors independently reviewed the results of the preliminary searches. Any discrepancy in article selection was resolved by consensus and discussion. Studies included met the following criteria: (i) studies reporting data on EUS-guided TA of the spleen, (ii) prospective and retrospective scientific studies enrolling at least five patients, (iii) studies reporting splenic EUS-TA of patients >18 years old, (iv) studies reporting data about the accuracy of EUS-TA of splenic lesions, (v) studies reporting data about the adequacy of the sample obtained using EUS-TA, and (vi) studies reporting data about adverse events related to splenic EUS-TA. Studies were included irrespective of the needle design and size, the EUS-TA technique used, and the route of EUS-TA access. We excluded (i) studies reporting data on EUS-TA of ectopic/accessory spleen or splenosis, (ii) studies reporting splenic EUS-TA on animals, (iii) studies that did not evaluate splenic EUS-TA diagnostic accuracy and sample adequacy, and (iv) case reports, letters, reviews, and comments.

Data extraction and quality assessment

Two authors (A.L., A.F.) independently recorded the data using a standardized form; any disagreement was resolved by consulting a third reviewer. The following data from each study were extracted: first author’s name, country of origin, year of publication, study design, study population, patients’ age and gender, EUS description of splenic lesion, size of splenic lesion, needle design and size, sampling technique with or without fanning technique, number of passes, material analysis (histology, cytology, bacteriology, or biochemical test), prevalence of malignant disease, and incidence of adverse events. The sensitivity, adequacy, and accuracy of splenic EUS-TA were extracted from the reported data.

The quality of included studies was rated by two reviewers independently (A.L., A.F.) based on the Newcastle–Ottawa scale for non-randomized studies [19]. Disagreements were solved by discussion and following a third opinion (P.F.).

Definitions

Sample adequacy was defined as the presence of tissue sample adequate for pathological analysis. Diagnostic accuracy was defined as the concordance between EUS-TA result and the gold-standard diagnosis. The gold-standard diagnosis was obtained with surgery, clinical and radiological follow-up, and/or pathological evaluation on EUS-TA samples. Adverse events should be defined as any occurring events that alter the usual patient management, complicating the diagnostic and therapeutic outcomes. The safety profile was defined as the incidence of adverse events among all procedures performed.

Statistical analysis

Study outcomes were pooled through a random-effects model based on the DerSimonian and Laird test, and results are presented as rates or pooled mean and 95% confidence interval (CI), where appropriate. The presence of heterogeneity was calculated through I^2 tests with $I^2 < 20\%$ interpreted as low-level heterogeneity. Any potential publication bias was verified through visual assessment of funnel plots. Sensitivity analysis was conducted according to (i) needle size (whether 22G, 25G or 19G) and (ii) study design (prospective vs retrospective studies). All statistical analyses were conducted using OpenMeta [Analyst] software. For all calculations, a two-tailed P-value of <0.05 was considered statistically significant.

Results

Literature search and population characteristics

A total of 1,007 articles were identified by using the described search strategy. After reading the title and the abstract, 64 full-text records were screened. Ultimately, six studies were

included in the qualitative and quantitative analysis. The details of the selection process and study flow chart are presented in Figure 1. Three studies were prospective, while the remaining had a retrospective design.

The quality of the included studies is presented in Supplementary Table 1. In detail, three studies accomplished all criteria for patients' selection, while the other three appeared sub-optimal. Four studies showed optimal quality in study outcomes domain, while two studies did not completely report the study outcomes (specimen accuracy in one case and prevalence of malignant conditions).

Table 1 describes the characteristics of the included studies. In total, 62 patients (35 male) were finally included; mean age was 54 years. The mean size of the splenic lesions was 36.6 mm. Twenty patients (32.3%) had a malignant disease of the spleen. Three studies included only patients with splenic focal solid lesions: one study dealt with diffuse parenchymal diseases, one study included patients with both focal solid and diffuse parenchymal conditions, and one final study included both solid and cystic splenic lesions. In all the six studies, authors performed cytological analysis on tissue samples obtained using EUS-TA. Further analyses performed in different studies, such as histology, flow cytometry, and bacteriology, are shown in Table 1.

All studies were conducted using EUS fine-needle aspiration (EUS-FNA) needles. The needle size was 19G in 7 cases (11.3%), 22G in 50 cases (80.6%), and 25G in the remaining 5 cases (8.1%). A mean of 2.62 (range, 1.95–3.28) needle passes was performed; significant heterogeneity was observed ($I^2 = 97.3\%$) among studies (Supplementary Figure 1) in this respect. Most splenic lesions (30/62, 48.4%) were lymphomas or other lymphoproliferative disease, while focal splenic tuberculosis (13/62, 21.0%), sarcoidosis (8/62, 12.9%), abscesses (4/62, 6.4%), cyst (4/62, 6.4%), solid tumor metastasis (2/62, 3.2%), and benign unspecified tumor (1/62, 1.6%) accounted for the remaining lesions.

Diagnostic performance

Pooled specimen adequacy (6 studies, 62 patients) was 92.8% (95% CI, 86.3%–99.3%) with very low heterogeneity ($I^2 = 12.5\%$). A forest plot for pooled adequacy is shown in Figure 2.

Pooled diagnostic accuracy (5 studies, 47 patients) of EUS-TA for the diagnosis of lesions of the spleen was 88.2% (95% CI, 79.3%–97.1%); no heterogeneity among studies was found ($I^2 = 0.0\%$). A forest plot for pooled accuracy is shown in Figure 3.

Adverse events

The pooled incidence of adverse events (6 studies, 62 patients) was 4.7% (95% CI, 0.4%–9.7%) with no heterogeneity ($I^2 = 0.0\%$). A forest plot is shown in Figure 4. Among all included studies, only one adverse event was reported; in detail, one patient with a splenic pseudocyst presented massive bleeding due to a splenic artery pseudoaneurysm 7 days after EUS-TA.

Sensitivity analysis and heterogeneity

Heterogeneity between the sample adequacy of the included studies was very low ($I^2 = 12.4\%$). A sensitivity analysis is shown in Supplementary Table 2. The study design (retrospective vs prospective) and EUS-FNA needle size (19G, 22G, and 25G) have been tested. Retrospective studies ($I^2 = 64.3\%$) and 22G EUS-FNA needle ($I^2 = 27.1\%$) appeared to be responsible for the observed heterogeneity.

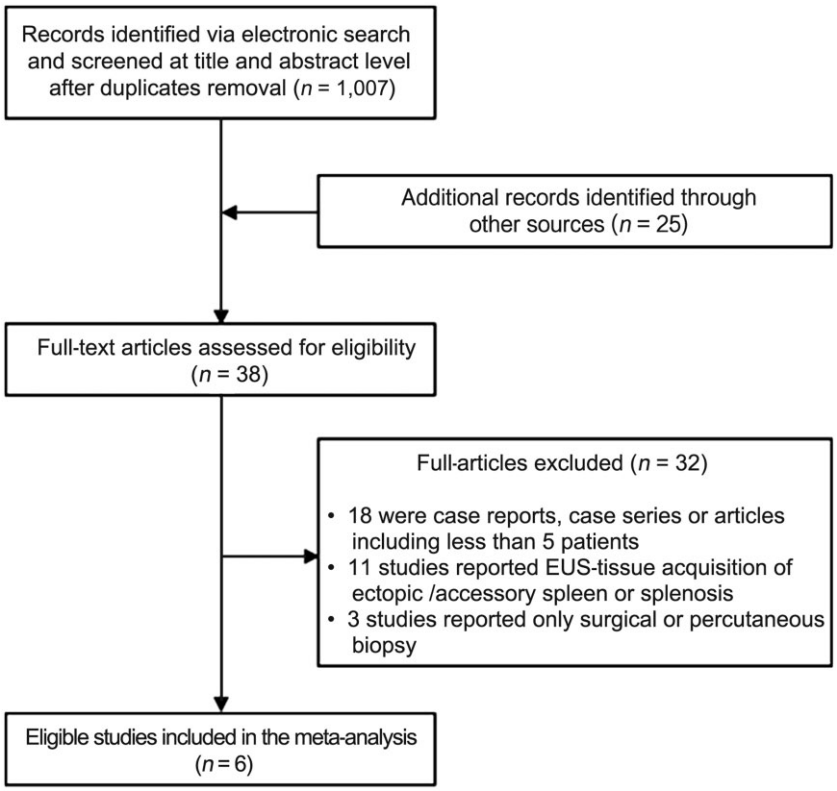

Figure 1. Study flow chart

Table 1. Characteristics of studies assessing the performance of endoscopic ultrasound-guided tissue acquisition of the spleen

Reference	Affiliation, country	Study design	Study period	Clinical indication	Needle size	Technique, fanning	**No. of passes** (mean ± SD)	Study population	**No. of males** (%)	**Age, years** (median [range])	Lesion size, mm
Fritscher-Ravens A *et al.* Am J Gastroenterol 2003 [16]	Royal London Hospital, United Kingdom	Prospective	1997–2001	Focal solid lesions	22 gauge	N/A	2.7 ± 0.9	12	7 (58.3%)	32 [19–68]	14 [8–42]
Eloubeidi M *et al.* Endoscopy 2005 [15]	University of Alabama at Birmingham, USA	Prospective	2000–2003	Focal solid lesions	22 gauge	N/A	4.5 ± 0.5	6	4 (66.6%)	58.5 [41–82]	45 ± 31
Iwashita T *et al.* Endoscopy 2009 [17]	Gifu University Hospital, Japan	Prospective	2004–2007	Focal solid lesions	19 gauge	N/A	2.4 ± 0.5	5	1 (20.0%)	64 [50–71]	53 ± 22
Rana SS *et al.* Ann Gastroenterol 2017 [14]	Postgraduate Institute of Medical Education and Research, India	Retrospective	2011–2017	Focal solid and cystic lesions	22 gauge (no. 13); 25 gauge (no. 2); 19 gauge (no. 1)	Suction, N/A	1.5 ± 0.5	16	11 (68.8%)	35.5 [28–43]	33 ± 30
Mosquera-Klinger G *et al.* Rev Esp Enferm Dig 2020 [13]	Hospital Pablo Tobón Uribe Medellín, Colombia	Retrospective	2019	Diffuse parenchyma and focal solid lesions	22 gauge (no. 14); 19 gauge (no. 1)	Slow-pull, No	2.7 ± 0.7	15	6 (40.0%)	67 [44–86]	38 ± 21
Niiya F *et al.* Endoscopy Int Open 2021 [18]	Showa University Fujigaoka Hospital, Japan	Retrospective	2016–2019	Diffuse parenchyma	22 gauge (no. 5); 25 gauge (no. 3)	Slow-pull and suction, no	2.0 ± 0.0	8	6 (75.0%)	66.8 [51–79]	N/A

SD, standard deviation; N/A, not available; mm, millimeter.
The values of lesion size, main axes, are presented as median with range or mean ± standard deviation.

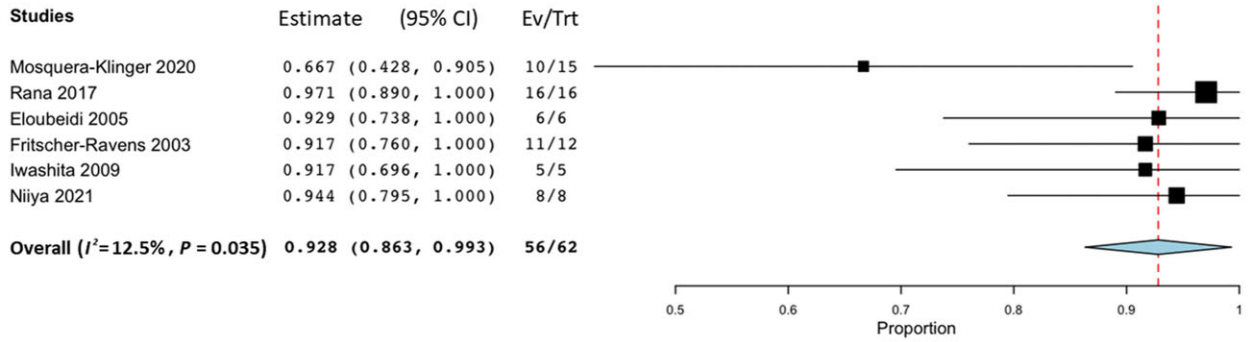

Figure 2. Pooled estimates for sample adequacy. Study outcomes were pooled through a random-effects model based on the DerSimonian and Laird test, and results are expressed as rates or pooled mean and 95% confidence interval (CI).

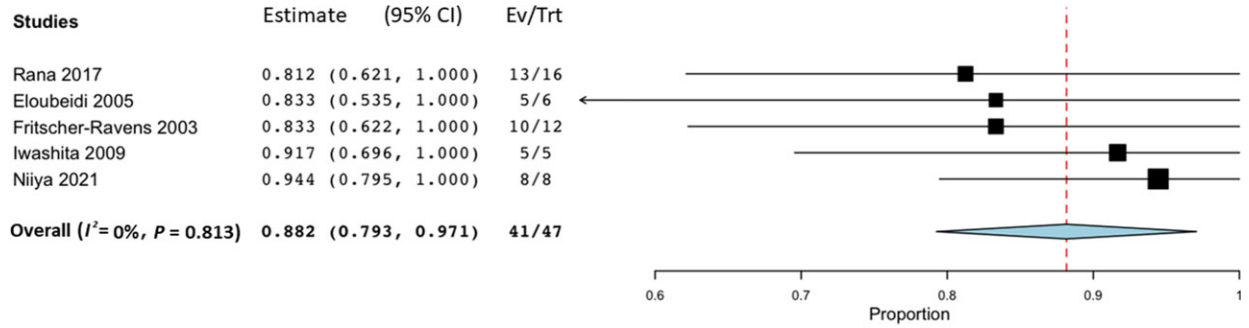

Figure 3. Pooled estimates for sample accuracy. Study outcomes were pooled through a random-effects model based on the DerSimonian and Laird test, and results are expressed as rates or pooled mean and 95% confidence interval (CI).

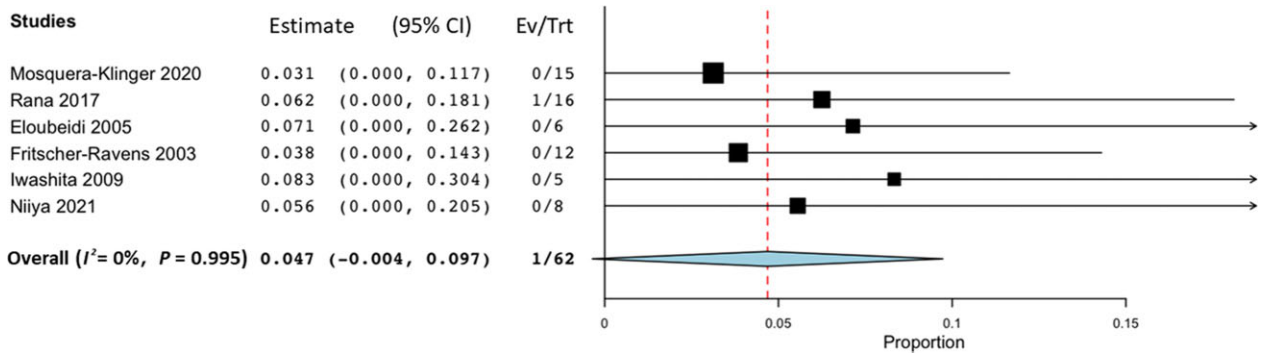

Figure 4. Pooled estimates for incidence of adverse events. Study outcomes were pooled through a random-effects model based on the DerSimonian and Laird test, and results are expressed as rates or pooled mean and 95% confidence interval (CI).

Discussion

Our meta-analysis showed 93% overall adequacy and 88% overall diagnostic accuracy for EUS-guided TA of the spleen. In comparison to available literature evidence, EUS-TA showed higher diagnostic accuracy than percutaneous image-guided FNA (sensitivity 87%, specificity 97%), but it had lower diagnostic accuracy than a percutaneous image-guided core needle biopsy [2–5].

It is possible to perform an accurate, high-resolution examination of the spleen from the stomach using EUS without the interposition of other organs. EUS-TA was initially reported for the characterization of small splenic lesions, taking advantage of the optimal real-time visualization of the parenchyma and its vascular architecture. The indications of EUS-TA have subsequently expanded to include both focal and diffuse spleen abnormalities [1].

Based on literature data, percutaneous image-guided core needle biopsy of the spleen has sensitivity and specificity of ~87% and ~97%, respectively. However, when coagulopathy or other risk factors for bleeding are present, cytology by percutaneous FNA may be the only option available at the expense of sensitivity and specificity, which may be decreased to 84% and 92%, respectively. EUS-TA has been used to overcome the limitations of percutaneous sampling with the theoretical advantage of a superior safety profile [2–5].

Although EUS-TA cytology may be sufficient for the diagnosis of lymphomas, which represent the most common causes of focal splenic lesions, it is very limited for the complete characterization of lymphoproliferative disorders

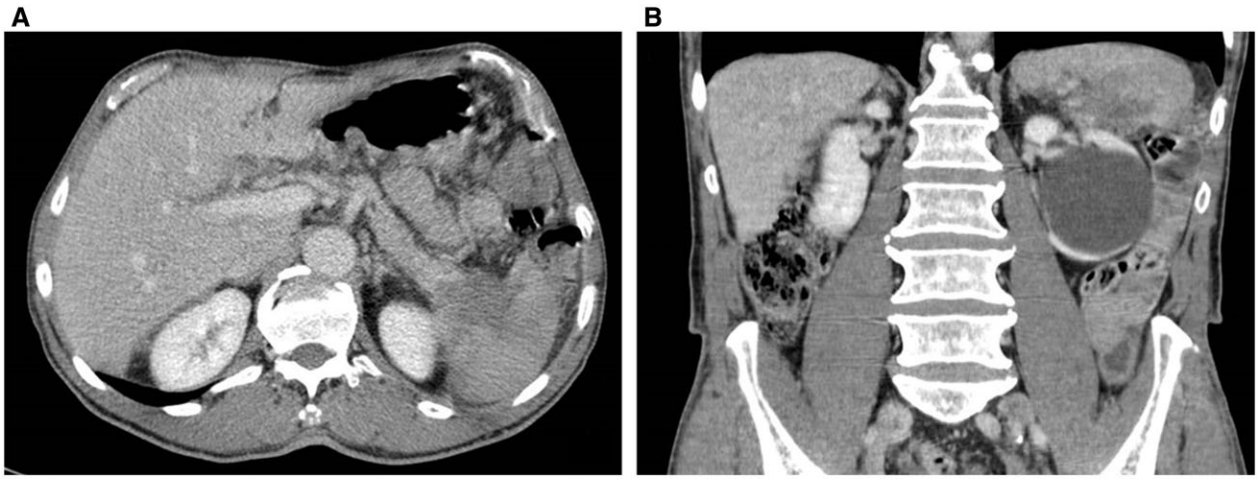

Figure 5. Computed tomography scan showing splenic B-cell lymphoma infiltrating the pancreatic tail from the splenic hilum. (A) axial plane; (B) coronal plane.

with immunohistochemistry (Figure 5). Thus, the use of flow cytometry on EUS-TA specimens has improved the diagnostic ability of this technique. Furthermore, the employment of large-gauge needles may help to overcome the limitations of EUS-TA, especially for the diagnosis of lymphoma subtypes, which is essential for the treatment strategy [6–8].

Our meta-analysis showed that about two passes were statistically significant to obtain diagnostic specimens. Fine needles of different sizes were used in the studies, with the 25G needle showing higher sensitivity and diagnostic accuracy than 22G and 19G needles (100% vs 90.8% and 88.1%, respectively). A further advantage of EUS-TA is the possibility to perform the "fanning technique" that allows sampling of multiple areas during each pass, potentially ensuring fewer passes to establish the diagnosis [13–18].

The overall complication rate of percutaneous image-guided TA was reported at 4.2% (1.9% for core needle biopsy and 1.3% for FNA cytology). The main adverse events were bleeding and pneumothorax due to the interposition of adjacent organs such as the ribs, pleura, lungs, kidneys, and the colon splenic flexure. Obesity, ascites, recent abdominal surgery, and the presence of intestinal gas represent risk factors for adverse events [13–18].

We found a similar rate of adverse events for splenic EUS-TA amounting to 4.7%. Rana *et al.* [14] reported a massive gastrointestinal bleeding from a splenic artery pseudoaneurysm 7 days after the EUS procedure that was successfully treated with surgery.

On the other hand, even though surgical splenectomy remains the reference standard for the diagnosis of indeterminate splenic lesions detected using imaging, it showed a higher rate of complications than EUS-guided and image-guided TA. Not only may it predispose patients to infection and thrombosis, but it also showed morbidity from 8.6% to 37% and mortality in $\leq$2.9% of cases.

The present study shows several limitations. First of all, the entire amount of included population appears relatively small. Moreover, $\leq$50% of included studies have a retrospective design. Even though low heterogeneity was observed in pooled adequacy and accuracy, significant heterogeneity was found among the included studies in terms of EUS-FNA needle size and passes, and indication for TA (diffuse disease, focal solid or cystic lesions). Since only one study has been performed using rapid on-site evaluation (ROSE) [15], no comparison between studies performed with and without ROSE is possible. Finally, this meta-analysis does not present the ability to quantify the technical success rate for spleen EUS-TA.

In conclusion, spleen EUS-TA represents a safe technique with high diagnostic adequacy and accuracy. It may be considered a valid alternative to the percutaneous approach, especially for focal lesions in order to increase the technical success rate [1].

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

A.L., A.C., and F.M. wrote the paper. A.F., S.F.C., and R.M.Z. designed the study protocol and performed the literature search and statistical analysis. N.B., B.M., A.O., and P.F. revised the manuscript for pivotal intellectual contents. All authors revised the manuscript and approved the final version of the manuscript.

Acknowledgements

None.

Conflict of Interest

The Authors declare no conflict of interest.

References

1. Trenker C, Görg C, Freeman S *et al.* WFUMB position paper-incidental findings, how to manage: spleen. *Ultrasound Med Biol* 2021;**47**:2017–32.
2. Olson MC, Atwell TD, Harmsen WS *et al.* Safety and accuracy of percutaneous image-guided core biopsy of the spleen. *AJR Am J Roentgenol* 2016;**206**:655–9.
3. McInnes MD, Kielar AZ, Macdonald DB. Percutaneous image-guided biopsy of the spleen: systematic review and meta-analysis of the complication rate and diagnostic accuracy. *Radiology* 2011;**260**:699–708.
4. Sidhu PS, Brabrand K, Cantisani V *et al.* EFSUMB guidelines on Interventional Ultrasound (INVUS), Part II: Diagnostic

ultrasound-guided interventional procedures (long version). *Ultraschall Med* 2015;**36**:E15–35.
5. Sammon J, Twomey M, Crush L *et al*. Image-guided percutaneous splenic biopsy and drainage. *Semin Intervent Radiol* 2012;**29**:301–10.
6. Polkowski M, Jenssen C, Kaye P *et al*. Technical aspects of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline—March 2017. *Endoscopy* 2017;**49**: 989–1006.
7. Jenssen C, Hocke M, Fusaroli P *et al*. EFSUMB guidelines on Interventional Ultrasound (INVUS), Part IV: EUS-guided interventions: general aspects and EUS-guided sampling (long version). *Ultraschall Med* 2016;**37**:E33–76.
8. Lisotti A, Frazzoni L, Fuccio L *et al*. Repeat EUS-FNA of pancreatic masses after nondiagnostic or inconclusive results: systematic review and meta-analysis. *Gastrointest Endosc* 2020; **91**:1234–41.
9. Facciorusso A, Sunny SP, Del Prete V *et al*. Comparison between fine-needle biopsy and fine-needle aspiration for EUS-guided sampling of subepithelial lesions: a meta-analysis. *Gastrointest Endosc* 2020;**91**:14–22.
10. Facciorusso A, Mohan BP, Crinò SF *et al*. Contrast-enhanced harmonic endoscopic ultrasound-guided fine-needle aspiration versus standard fine-needle aspiration in pancreatic masses: a meta-analysis. *Expert Rev Gastroenterol Hepatol* 2021; **15**:821–8.
11. Crinò SF, Ammendola S, Meneghetti A *et al*. Comparison between EUS-guided fine-needle aspiration cytology and EUS-guided fine-needle biopsy histology for the evaluation of pancreatic neuroendocrine tumors. *Pancreatology* 2021;**21**:443–50.
12. Facciorusso A, Crinò SF, Muscatiello N *et al*. Endoscopic ultrasound fine-needle biopsy versus fine-needle aspiration for tissue sampling of abdominal lymph nodes: a propensity score matched multicenter comparative study. *Cancers (Basel)* 2021;**13**:4298.
13. Mosquera-Klinger G, de la Serna Higuera C, Bazaga S *et al*. Endoscopic ultrasound-guided fine-needle aspiration for splenomegaly and focal splenic lesion: is it safe, effective and necessary? *Rev Esp Enferm Dig* 2020;**112**:355–9.
14. Rana SS, Sharma V, Sharma R *et al*. Safety and utility of endoscopic ultrasound-guided fine-needle aspiration of focal splenic lesions: a retrospective analysis. *Ann Gastroenterol* 2017;**30**:559–63.
15. Eloubeidi MA, Varadarajulu S, Eltoum I *et al*. Transgastric endoscopic ultrasound-guided fine-needle aspiration biopsy and flow cytometry of suspected lymphoma of the spleen. *Endoscopy* 2006;**38**:617–20.
16. Fritscher-Ravens A, Mylonaki M, Pantes A *et al*. Endoscopic ultrasound-guided biopsy for the diagnosis of focal lesions of the spleen. *Am J Gastroenterol* 2003;**98**:1022–7.
17. Iwashita T, Yasuda I, Tsurumi H *et al*. Endoscopic ultrasound-guided fine needle aspiration biopsy for splenic tumor: a case series. *Endoscopy* 2009;**41**:179–82.
18. Niiya F, Takano Y, Azami T *et al*. Usefulness of endoscopic ultrasound-guided fine needle aspiration for splenic parenchyma in patients suspected of having primary splenic malignant lymphoma. *Endosc Int Open* 2021;**9**:E96–101.
19. Wells GA, Shea B, O'Connell D, *et al*. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (21 May 2022, date last accessed).