



Alimentary Tract

Ultrasound-guided percutaneous biopsy for diagnosis of gastrointestinal lesions

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ABSTRACT

Background and aims: Endoscopic examination is not always sufficient for the diagnosis of gastrointestinal masses. This study assessed the diagnostic accuracy and safety of ultrasound-guided percutaneous biopsy of gastrointestinal lesions.

Methods: This retrospective study evaluated 114 patients who underwent ultrasound-guided biopsy of gastrointestinal masses with a 18G needle. Thirty-two of these patients underwent a 22G fine-needle biopsy for cytology. Histology was compared with a composite standard of reference for diagnosis (i.e. post-surgery histological evaluation in 73 cases and computed tomography or magnetic resonance scan findings, together with a compatible clinical follow-up for at least 24 months, in the remaining 41 cases). Safety was assessed by recording side effects for up to 4 h after the procedure.

Results: Of the 114 lesions evaluated, 112 were malignant (98.2%) and 2 benign (1.8%). Specimens were adequate for histology in all but one case. Specimens were obtained from the stomach ($n=38$; 33.3%), small bowel ($n=36$; 31.6%) and colon ($n=40$; 35.1%). Diagnosis was correct in 113/114 cases (99.1%). Sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy were 99.1%, 100%, 100%, 66%, and 99%, respectively. One of the 114 patients (0.9%) bled from a gastric GIST.

Conclusions: Ultrasound-guided percutaneous biopsy of gastrointestinal lesions is a valid alternative when diagnosis of a gastrointestinal mass cannot be obtained with an endoscopic procedure.

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1. Introduction

Endoscopy is the first level procedure for the diagnosis of gastrointestinal (GI) wall lesions since it allows obtaining multiple biopsies as well as a direct detection of the lesion. However, lesions that are mainly located within the submucosa or subserosa, such as lymphoma or gastrointestinal stromal tumours (GIST), may be difficult to diagnose with endoscopy [1]. In these cases endoscopic ultrasonography (EUS) and EUS-guided biopsies are effective alternative approaches [2]. However, a EUS-guided biopsy is not always feasible for gastrointestinal (GI) masses either because of the lesion location (i.e. colon or small-bowel) or because of GI lumen stenosis. Moreover, a EUS-guided biopsy may require anesthesiological care even though, according to the data of a large series of EUS examinations, this may be necessary in less than 5% of the cases [3]. Small bowel lesions cannot be studied by conventional endoscopy and need either videocapsule endoscopy [4] or double-balloon

enteroscopy (DBE). Videocapsule endoscopy does not allow for biopsy collection. DBE allows for biopsy collection, however it is not widely available, it is time consuming and not completely free of risk for the patient.

Ultrasonography (US) is an effective diagnostic procedure both for neoplastic and inflammatory GI lesions, which present as "target" or "bull's eye" lesions or "pseudo-kidney" masses [5–7]. US is a non-invasive, cost-effective, fast and safe technique; it does not require the use of ionizing radiation or any other preparation for the patient. Moreover, US-guided percutaneous biopsy is a widely accepted procedure in diagnosing lesions occupying the abdominal and retroperitoneal space. US-guided biopsies have mainly been performed in the diagnosis of lesion located in solid abdominal and retroperitoneal organs, such as liver, pancreas, spleen, kidney and lymph nodes [8], with a high diagnostic accuracy, a low complication rate and a very low mortality rate [9–13]. However, a number of reports suggest the possibility of diagnosing GI neoplasia by US-guided biopsy [14–16].

We hypothesized that US-guided percutaneous biopsy of GI tract lesions might serve as a valid alternative diagnostic approach for patients in whom specimens of GI tract lesions suitable for histology cannot be obtained by endoscopy. This single-centre study

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was therefore aimed at evaluating the feasibility, diagnostic accuracy and safety of US-guided percutaneous biopsies of GI tract lesions.

2. Materials and methods

This is a single-centre retrospective study based on prospectively collected data of 114 consecutive patients. Patients were referred to our Ultrasonography Section from both the Medical and Surgical Departments of the Second University of Naples between January 2000 and January 2012. Patients were referred to perform a US-guided percutaneous biopsy of GI wall lesions that were well visualized at US and for which a diagnosis had not been reached due to the following reasons: the lesion was not endoscopically accessible (i.e. localized between the Treitz ligament and ileocecal valve, or after a stenosis, $n = 64$); the endoscopic biopsy was repeatedly (2–3 times) negative ($n = 40$); contraindications to perform endoscopy due to severe cardiac disease ($n = 10$). Final diagnosis was based either on histology of surgery specimens, available for 73 cases, or on a surrogate standard of reference for diagnosis (used for the remaining 41 cases), which included computed tomography (CT) or magnetic resonance imaging (MRI) scan findings, together with a compatible clinical follow-up of at least 24 months. For all cases we used a real-time ultrasound scanner (ESAOTE TECHNOS MPX), with multi-frequency convex probe (2.5–5 MHz) and side adapter (20–30° variable angle).

Biopsies were performed both in inpatients and outpatients. The examination took place after overnight fast. We performed the biopsies without bowel preparation, antibiotic prophylaxis or local anaesthesia. A B-mode US exam and colour Doppler were preliminarily performed in all patients to evaluate the faster needle pathway and avoid vascular structures. We used large cutting needles (Biomoll 18G-HS) for histological evaluation. Additionally, for 32 patients in whom a lymphoproliferative disorder was suspected, we also used fine non-cutting needles (Ecojekt 22G-HS) for cytological analysis. In the cases examined since 2004 we preliminarily used second-generation contrasts (Sonovue) for masses larger than 5 cm, in order to avoid sampling in necrotic areas. Histological specimens were fixed in formalin, embedded in paraffin and then stained with haematoxylin–eosin. Further immunohistochemical analysis of the material was possible for specific indications. After biopsy patients were monitored by measuring blood pressure and pulse rate every 30 min during the 3–4 h following the procedure, as to evaluate possible complications. Contraindications to US-guided biopsy were the following: severe coagulative impairment (platelet count $\leq 40,000/\text{mm}^3$ and prothrombin time $\leq 40\%$), distension of bowel loops, and presence of vascular structures along the needle's pathway. We performed a mean of 1.2 passages (range 1–2) for both core and cytological sampling.

All patients provided written informed consent. The study was approved by the local institutional review board and was conducted according to the Declaration of Helsinki and its amendments, and the Good Clinical Practice guidelines.

2.1. Reference standard for the diagnosis of malignant vs benign disease

A final diagnosis of malignant or benign disease was made according to one of the following reference methods: (i) definite benign or malignant histological diagnosis based on surgical resection specimens from patients who underwent surgery ($n = 73$); (ii) histological findings with definite proof of malignancy in patients with unresectable tumours according to CT/MRI scan findings and compatible clinical follow-up ($n = 39$); (iii) histological findings without proof of malignancy and a minimum clinical follow-up of 24 months ($n = 2$).

Table 1

Final diagnosis in 114 patients with ultrasonographically visible GI tract lesions.

Lesion types	Stomach	Small bowel	Colon
Non-Hodgkin lymphoma	18 (15.7%)	16 (14.0%)	–
GISTs	14 (12.3%)	9 (7.9%)	–
Adenocarcinoma	5 (4.4%)	4 (3.5%)	37 (32.4%)
Metastases	–	5 (4.4%)	–
Undifferentiated carcinoma	1 (0.9%)	2 (1.8%)	–
Abscessualised carcinoma	–	–	1 (0.9%)
Endometriosis	–	–	1 (0.9%)
Bowel duplication	–	–	1 (0.9%)
Total	38 (33.3%)	36 (31.6%)	40 (35.1%)

2.2. Assessment of safety

In accordance with the guidelines of the Society of Interventional Radiology, major complication was defined as an unexpected event increasing the level of care and/or prolonged hospital state and/or permanent adverse sequelae. Any other event was considered a minor complication [17]. Safety was assessed in both inpatients and outpatients; timing and severity of complications were evaluated. Complications were assessed for up to 6 h after procedure. Additionally, patients were instructed to contact the study physician for any symptom occurring up to 48 h after discharge.

2.3. Statistical analysis

Descriptive data are shown as percentages. Normally distributed variables are shown as mean $\pm$ standard deviation (SD) and range. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy (DA) of US-guided percutaneous biopsy of GI tract lesions have been determined and are shown as percentage and 95% confidence interval (CI). To assess the agreement between US-guided biopsy-based diagnosis and composite standard of reference-based diagnosis (i.e. surgery + compatible imaging and clinical follow-up) of GI tract malignant lesions we calculated the Cohen's kappa correlation coefficient using SPSS 19.0 Software (IBM Corporation, NY).

3. Results

Overall 114 patients were included (55.3% males; median age 68 years range 55–80 years), and 114 biopsy specimens of the GI tract were obtained. This represents 2.4% (114/4750) of the total number of US-guided biopsies performed during the study period, while the remaining biopsies were performed on organs other than the GI tract. In 32 patients we also obtained a fine-needle biopsy for cytofluorimetry, since a lymphoproliferative disorder was suspected. Both core and fine-needle biopsies were feasible in 100% of the cases. None of the cases presented a GI lesion that was ultrasonographically visible but not accessible for biopsy because deeply seated in the abdomen or partially masked by bowel content and/or gas. A sample suitable for pathological evaluation was obtained in 113/114 (99.1%) patients. Only in one case (small bowel non-Hodgkin lymphoma) a second biopsy was required to perform further immunohistochemical evaluation. In the 32 cases in which a fine-needle biopsy was performed, all samples were suitable for cytofluorimetry. Specimens were obtained from the stomach ($n = 38$; 33.3%), small bowel ($n = 36$; 31.6%), and colon ($n = 40$; 35.1%). The average size of the US visible lesions was 35 ± 16 mm (range 20–80 mm), while the average size of the biopsy specimens was 22 ± 10 mm (range 15–40 mm). Final diagnosis based on a composite standard of reference for diagnosis was malignancy in 112/114 (98.2%) cases and benign lesion in 2/114 (1.8%) cases (Table 1). The 2 benign lesions were endometriosis of the sigmoid colon and intestinal duplication. US-guided biopsy correctly

diagnosed all the malignant lesions except for one case of gastric adenocarcinoma, in which the pathological evaluation of the sample obtained by US-guided biopsy gave a falsely negative result (i.e. chronic gastritis). Both benign lesions were correctly diagnosed by US-guided biopsy. Sensitivity, specificity, PPV, NPV and DA of US-guided percutaneous biopsy of GI masses were 99% (111/112; 95% CI, 97–100%), 100% (2/2; 95% CI, 100–100%), 100% (111/111; 95% CI, 100–100%), 66% (2/3; 95% CI, 13–100%), and 99% (113/114; 95% CI, 97–100%), respectively. The level of agreement between US-guided biopsy-based diagnosis and composite standard of reference-based diagnosis, as assessed by Cohen's kappa correlation coefficient, was 0.796 ($p < 0.0001$). We observed no deaths after biopsy, and the procedure was well tolerated in 113 cases. Only one patient presented with a major complication, i.e. melena 24 h after procedure due to bleeding from gastric GIST. Bleeding was controlled by endoscopically positioned metallic clips.

4. Discussion

This study shows that US-guided percutaneous biopsy of GI tract lesions may represent a valid and safe diagnostic procedure in those cases in which the location of the GI lesion or the impossibility to perform endoscopy do not allow for adequate sampling for histology. Particularly, in our study, diagnosis based on US-guided biopsy was correct in 113/114 cases, with a 99% diagnostic accuracy.

The role of US-guided biopsies in the diagnosis of GI tract lesions non-easily accessible with conventional techniques has already been suggested by a number of authors [14,15,18]. Moreover, core biopsy of hollow organs of the GI tract has been demonstrated as a useful method for obtaining specimens suitable for pathological examination when endoscopic methods have failed [19,20]. Our study confirms previously published data regarding sensitivity, specificity and diagnostic accuracy of this procedure [14,21]. The results obtained in this study are also comparable with those described by Iglesias-Garcia et al. who, in a similar number of patients in a multicentre study, demonstrated that fine-needle biopsy of GI tract lesions yields samples adequate for pathological evaluation and has a high diagnostic accuracy [22]. Additionally, Tombesi et al. have recently performed a retrospective study on 45 consecutive patients who underwent US-guided biopsies of GI lesions. No procedure-related complications were described in their patients and US-guided biopsy allowed preventing unnecessary surgical exploration in 10 cases. The authors also used clinical-instrumental follow-up when surgical specimens were not available and reported high values of sensitivity (97.5%), specificity (100%), PPV (100%) and DA (97.7%) [23].

The number of studies regarding US-guided biopsies of GI masses is by far lower than those regarding biopsies of solid organs such as liver. Therefore, our study, which to our knowledge is conducted in the largest single-centre cohort of patients described in the literature, provides solid evidence in favour of US-guided percutaneous biopsy of GI masses for diagnosis of GI lesions that cannot be appropriately diagnosed by an endoscopic-based procedure.

The needle's size to be used for biopsy of GI tract lesions (i.e. 18G vs 22G needles) has been a matter of debate [24]. In this study the main reason for using an 18G needle rather than a 20–22G needle is that, in our experience, the 18G needle yields more frequently biopsy samples adequate for histology, while being as safe as the 20–22G needle. Additionally, the larger tissue specimens obtained with the 18G needle are more adequate for performing supplementary evaluations (such as immunohistochemistry) than the specimens obtained with fine-needle aspiration techniques. Partially supporting this latter observation, Marco-Doménech et al. found, in a study aimed at evaluating the safety and efficacy of US-guided percutaneous biopsy of GI lesions, that a specific diagnosis

was obtained in 40/42 (95.2%) core specimens obtained with an 18G needle vs the 16/35 (45.7%) obtained with a fine-needle (i.e. 22G) aspiration biopsy, with only one immediate serious complication being recorded [18]. Also, Tudor et al. used an 18G needle for US-guided percutaneous biopsy of bowel wall lesions in 10 patients and obtained a correct diagnosis with no complications in any of the cases [24].

Safety is an important issue when dealing with invasive procedures. The possibility of complications such as haemorrhage, peritonitis, sepsis or needle track seeding of malignancy has limited the application of percutaneous biopsy in GI wall lesions. However, a number of studies have demonstrated that US-guided percutaneous core biopsy of GI lesions is not associated with a significant rate of complications [18,19,24]. Similarly, several studies described no complications secondary to fine-needle biopsy of GI masses. In particular, Ballo and Guy [14] and Carson et al. [15] did not experience any immediate or delayed complications following the procedure, thus supporting the safety of percutaneous GI biopsy. Other authors experienced a limited number of complications such as one case of hemoperitoneum, one of sepsis [21], and one of bile peritonitis [18]. In our study of 114 patients we had only one major complication due to the bleeding of a gastric GIST that was promptly endoscopically controlled by positioning metallic clips. Therefore, our study strongly supports the safety of US-guided percutaneous biopsy of GI tract lesions as far as immediate complications are concerned. However, because we have no data regarding long-term follow-up either in the surgically removed or the unresectable tumour groups, we cannot draw any conclusion regarding long-term safety of the procedure.

One may argue that the number of cases of gastric (6 cases) and colon (37 cases) carcinoma that were not diagnosed by endoscopy was too high. However, with regard to the gastric carcinoma cases, in 4 patients endoscopy was not possible due to the poor health conditions of the patients, in 1 case the patient refused to undergo a second endoscopy after the first had not been diagnostic, and in the remaining case histology was repeatedly negative. However, this was a case of infiltrating undifferentiated carcinoma with neoplastic tissue mainly located in the submucosa with a histologically normal superficial mucosa (Fig. 1), thus partially explaining the negative results of the endoscopic biopsies. With regard to the 37 cases of colon carcinoma that were not diagnosed by endoscopy, in 18 patients stenosis prevented optimal sampling of neoplastic tissue, in 6 cases colonoscopy was not possible due to severe comorbidity (i.e. severe ischemic heart disease), and in the 13 remaining cases histology was negative in 2 subsequent colonoscopies. Therefore, over a 12-year period, there was approximately 1 case of histologically false negative colon cancer per year.

We recognize that the present study has some limitations. First, the results cannot be extended to all GI lesions not accessible to conventional endoscopy or EUS, because lesions have anyway to be visualized by US. Secondly, comparison of the pathological results of US-guided biopsies with histology from surgical specimens should have been the standard reference of diagnosis. This could be carried out for the majority of cases (i.e. 73/114 patients), whereas for the remaining 41 patients CT/MRI scan findings, together with a compatible clinical follow-up of at least 24 months, served as a surrogate standard of reference for diagnosis. Although not ideal, this method is a well-accepted reference standard [22].

In conclusion, based on this study, we can conclude that US-guided percutaneous biopsy is an effective procedure for diagnosis of GI tract lesions, with a high diagnostic accuracy and an almost null immediate complication rate. We postulate that this procedure could be satisfactorily and safely used for all lesions visualized in B mode, when previous endoscopy or EUS have not provided definite results, and for small bowel lesions when double-balloon enteroscopy is not available or when stenosis or clinical conditions



Fig. 1. (a) Ultrasonography (US) showing a “pseudo-kidney” image at the level of the gastric antrum (arrow) and (b) photomicrograph of an histological specimen obtained by US-guided biopsy. Haematoxylin–eosin staining (40×) showing normal appearing superficial mucosa (white arrow) and infiltrating undifferentiated carcinoma in the submucosa (black arrow).

(such as severe heart disease) contraindicate an endoscopic procedure.

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None.

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