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Value of endoscopic ultrasonography for upper gastrointestinal stromal tumors: A single center experience

Üst gastrointestinal stromal tümörlerde endoskopik ultrasonografinin değeri: Tek merkez deneyimi

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Background/aims: *Gastrointestinal stromal tumors are the rarely seen tumors of the gastrointestinal tract. The aim of the present study was to review the patients diagnosed as upper gastrointestinal stromal tumor by endoscopic ultrasonography.* ***Methods:*** *Twenty-five patients diagnosed as upper gastrointestinal stromal tumor, between 1999 and 2004, were reviewed retrospectively.* ***Results:*** *The reason for performing upper gastrointestinal system endoscopy was nonspecific upper gastrointestinal system symptoms in most (76%) of the patients. The other causes were upper gastrointestinal bleeding and dysphagia in 16% and 8% of the cases, respectively. Lesions were located in the stomach in 17 (68%), in the esophagus in six (24%), and in the duodenum in two (8%) patients. Endoscopic ultrasonographic evaluation revealed that all of the lesions arose from the muscularis propria. In 18 (72%) patients, tumors were less than 3 cm in diameter, homogeneous and hypoechoic in appearance with regular borders, concordant with benign tumor. In five (20%) patients, lesions had heterogeneous echoic appearance with anechoic spaces, two of which were larger than 3 cm and also showed irregular borders, suggesting malignancy. Surgical therapy was performed in five (20%) patients because of upper gastrointestinal bleeding or suspicion of malignancy by endoscopic ultrasonographic evaluation. Histopathological examination confirmed the diagnosis in all these patients.* ***Conclusions:*** *Endoscopic ultrasonographic evaluation is very useful in diagnosis and for choosing the therapeutic method for patients with upper gastrointestinal stromal tumor.*

Key words: Gastrointestinal stromal tumor, endoscopic ultrasonography, diagnosis

Amaç: *Gastrointestinal stromal tümörler gastrointestinal traktüsün nadir görülen tümörler indendir. Bu çalışmada endoskopik ultrasonografi ile üst gastrointestinal stromal tümör tanısı alan hastalarımızın değerlendirilmesi amaçlanmıştır.* ***Yöntem:*** *1999-2004 yılları arasında üst gastrointestinal stromal tümör tanısı alan 25 hasta retrospektif olarak irdelenmiştir.* ***Bulgular:*** *Olguların %76'sına nonspesifik üst gastrointestinal sistem yakınmaları, %16'sına üst gastrointestinal sistem kanaması, %8'ine ise disfaji nedeniyle üst gastrointestinal sistem endoskopisi uygulanmıştır. Lezyonların 17 (%68)'si midede, 6 (%24)'sı özofagusta ve 2 (%8/si de duodenumda saptanmıştır. Endoskopik ultrasonografik incelemede lezyonların tümünün muskularis propria tabakasından kaynaklandığı görülmüştür. Hastaların 18 (%72/inde benign tümörle uyumlu olarak, tümör çapının 3cm'den küçük, homojen ve hipoekoik yapıda ve düzgün kenarlı olduğu saptanmıştır. 5 (%20) hastada ise lezyonun heterojen eko yapıda ve anekoik alanlar içerdiği saptanmış, ayrıca bunların 2'sinin de maligniteyi düşündürecek şekilde 3cm'den büyük olup düzensiz kenarlara sahip olduğu dikkati çekmiştir. Endoskopik ultrasonografik değerlendirmede maligniteden kuşkulanılan veya üst gastrointestinal sistem kanaması ile başvuran 5 (%20) hastaya cerrahi tedavi uygulanmıştır. Bu hastaların tümünde histopatolojik olarak tanı doğrulanmıştır.* ***Sonuç:*** *Üst gastrointestinal stromal tümörlerin tanısında ve tedavi seçiminde endoskopik ultrasonografi oldukça yararlı bir inceleme yöntemidir.*

Anahtar kelimeler: Gastrointestinal stromal tümör, endoskopik ultrasonografi, tanı

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and may present from the lower esophagus to the anus, mostly from the stomach (1). The majority of these neoplasms are asymptomatic and are discovered incidentally during endoscopic or radiologic examinations. They occur in equal frequency in men and women, generally after the fifth decade (2-6). Most GISTs are benign, but around 15% are malignant (7). They

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are diagnosed immunohistochemically by positivity of a tyrosine kinase growth factor receptor (ckit: CD117) and usually absence of desmin (1, 8). Differential diagnosis of GISTs from the other mesenchymal tumors is important since a c-kit-selective tyrosine kinase inhibitor (imatinib mesylate) is available in metastatic or unresectable GISTs (9). Evaluation with endoscopic ultrasonography (EUS) is very useful in differential diagnosis of GISTs from other submucosal tumors such as lipomas, carcinoid tumors, etc. In this study, we review 25 patients with upper GISTs and discuss the usefulness of EUS in their diagnosis.

MATERIALS AND METHODS

Twenty-five patients diagnosed between 1999-2004 as upper GIST using EUS in the Gastroenterology Department of Ege University Medical School Hospital were reviewed retrospectively. All patients were referred for EUS because of the presence of suspected submucosal lesions on upper GI system endoscopy. EUS was performed with Olympus EU-M30 radial endoscopic ultrasound system. The diagnosis of GIST was based on typical EUS findings of GIST described as hypoechoic mass arising from muscularis propria. Patients with submucosal lesions were excluded when EUS findings were not sufficient for an accurate diagnosis of GIST.

RESULTS

Fifteen (60%) of 25 patients with upper GIST were male and 10 (40%) were female (age range: 22-74 years, average: 49.4+15.0 years). Upper GI system endoscopy was performed in 19 (76%) patients for nonspecific GI system symptoms, in four (16%) patients for upper GI system bleeding, and in two (8%) patients for dysphagia. Upper GI system endoscopy showed suspected submucosal lesions in all of the patients and they were referred for EUS thereafter. Figure 1 shows endoscopical appearance of a patient with GIST at the fundus of the stomach. Seventeen (68%) GISTs were located in the stomach, six (24%) in the esophagus, and two (8%) in the duodenum. Median size was 3.23+2.54 cm. Among those located in the stomach, corpus was the most common site. Details of tumor localizations are given in Table 1. Four (23.5%) of the tumors located in the stomach had ulceration on the surface. None of the GISTs located in the esophagus and duodenum was ulcerated.

Table 1. Localizations of upper gastrointestinal stromal tumors

Localization	n=25	Sublocalization	
Esophagus	6 (24%)	Upper	0 (0%)
		Middle	3 (50%)
		Lower	3 (50%)
Stomach	17 (68%)	Cardia	2 (11.8%)
		Fundus	2 (11.8%)
		Corpus	9 (52.8%)
		Antrum	4 (23.6%)
Duodenum	2 (8%)	Bulbus	2 (100%)

Endoscopic ultrasonography examination showed homogeneous and hypoechoic mass with regular borders, less than 3 cm in diameter, concordant with benign GIST in 18 (72%) patients (Figure 2, 3). Follow-up EUS examinations were planned in these patients. Table 2 shows the properties of the seven patients with a tumor size larger than 3 cm.

In five (20%) patients, lesions had heterogeneous echoic appearance with anechoic spaces. Three of these patients had upper GI bleeding. The lesions of the other two patients were 9 and 12 cm in size and also showed irregular borders, suggesting malignancy (Figure 4). Surgical therapy was performed in these five patients. GISTs were located in the stomach in all of them. Histopathological and immunohistochemical examinations confirmed the diagnosis of GIST. Malignant GIST was determined in two cases with irregular borders. Endoscopy revealed ulceration on the surface of the tumor in one of the two patients with histopathologi-

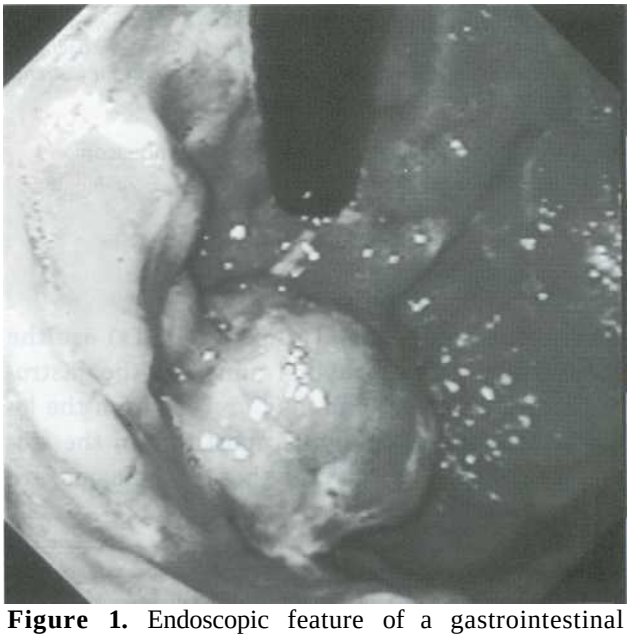

Figure 1. Endoscopic feature of a gastrointestinal stromal tumor localized at the fundus of the stomach

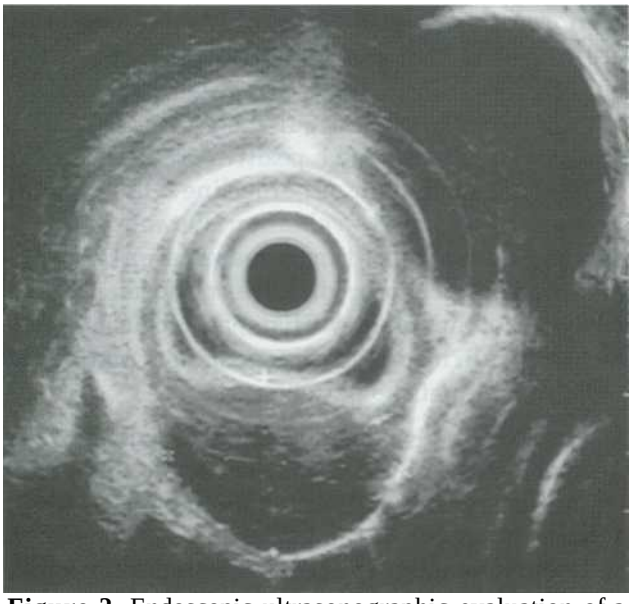

Figure 2. Endoscopic ultrasonographic evaluation of a gastrointestinal stromal tumor localized at the esophagus showed a hypoechoic, homogeneous mass arising from muscularis propria

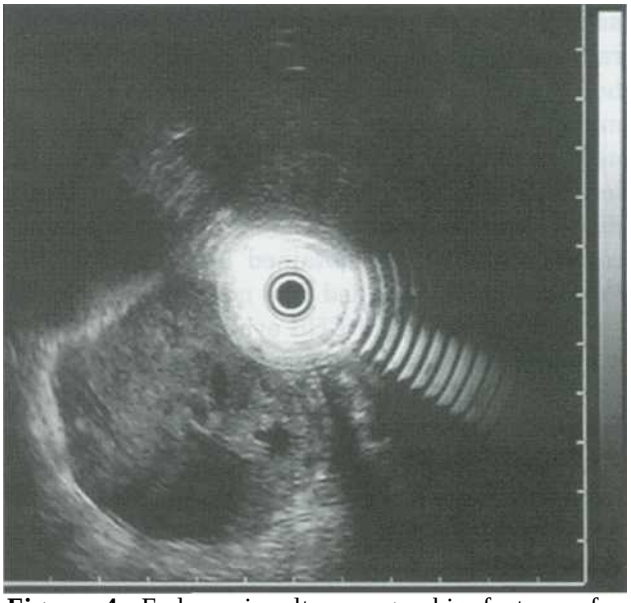

Figure 4. Endoscopic ultrasonographic feature of a malignant gastrointestinal stromal tumor at the stomach. Note the large heterogeneous mass with anechoic spaces and irregular borders suggesting malignancy

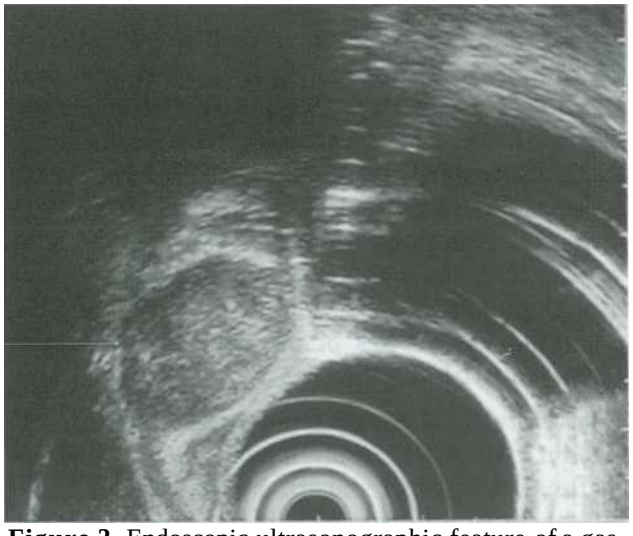

Figure 3. Endoscopic ultrasonographic feature of a gastrointestinal stromal tumor localized at the stomach. Arrow shows a mass arising from muscularis propria

cally proven malignant GIST. On the other hand, all of the operated patients who presented with upper GI bleeding (3 patients) had ulceration, and none of them showed malignancy findings on histopathological examination.

DISCUSSION

Endoscopy is the gold standard technigue for diagnosing lesions of the GI system. However, endoscopy and routine endoscopic biopsies are not sufficient for an accurate diagnosis of submucosal lesions of the GI system. Furthermore, non-invasive imaging methods such as transabdominal ultrasonography, computed tomography and magnetic resonance imaging give limited information regarding submucosal lesions. Suspected submucosal lesions at endoscopy can be caused by intramural

Table 2. Properties of the 7 patients with tumor size larger than 3 cm

Patient no	Tumor size (cm)	GI bleeding	Ulceration	Heterogeneous echogenity with anechoic spaces	Irregular borders	Operation	Histopathological malignancy
1	12			+	+	+	+
2	9	-	+	+	+	+	+
3	5	+	+	+	-	+	-
4	5	+	+	+	-	+	-
5	4.5	+	+	+	-	+	-
6	5			-	-	refused	?
7	4			-	-	refused	?

GI: Gastrointestinal

as well as extramural structures. The detailed ultrasound images obtained by EUS can clarify whether the submucosal lesion is caused by an intramural or extramural structure. EUS can also be used to identify the layer of origin of intramural lesions and classify lesions as cystic or solid. In addition, some indicators of malignancy for submucosal lesions can be obtained using EUS (7,10). Performing EUS-guided fine needle aspiration is another advantage of EUS evaluation (11). When a submucosal lesion is suspected during routine endoscopy, EUS evaluation has to be performed in order to exclude extramural or vascular lesions. Aggressive biopsy techniques using snares or puncture may be hazardous in these cases. In addition, a differential diagnosis is needed for intramural lesions.

Endoscopic ultrasonography hâs become an invaluable imaging modality for the clinical diagnosis of GIST and for differentiating these neoplasms from other submucosal lesions (7, İÖ, 12-16). At EUS, GISTs are characterized by a hypoechoic appearance and can be seen to originate from the fourth hypoechoic endosonographic layer (muscularis propria). One of the important questions in GlSTs concerns its possible malignancy. On histopathological examination, tumors that have mitotic activity counts exceeding 5 per 50 high power fields (HPF) are likely to be malignant. In contrast, tumors showing less than 5 per 50 HPF are likely to be benign. An additional benefit of EUS for GISTs is that it helps clinicians establish GISTs as malignant or benign. When imaging a GIST, EUS features that should be characterized include regularity of the extraluminal border, presence of cystic spaces, echogenic foci, heterogeneity and size (7,10,17, 18). An irregular extraluminal border is likely associated with an invasive tumor, cystic areas likely represent cellular necrosis, and echogenic foci are likely caused by fibrosis (7). The features most predictive of benign GISTs are regular margins, tumor size less than 3 cm and a homogeneous echo pattern (10). In this study, benign GISTs were diagnosed in 18 (72%) cases with homogeneous hypoechoic echo pattern, regular margins and tumor size smaller than 3 cm in diameter. In a prospective, multicenter study, Nickl et al. (19) found that EUS features that were predictive of malignancy in stromal cell tumors included: ulcerated mucosa, size of GIST greater than 3 cm, hypo- or hyperechoic foci, poorly defined margins, irregular shape, abnormal lymph nodes and high growth rate at follow-up EUS. Palazzo et al. (10) reported that the combined presence of two out of three EUS features (irregular extraluminal margins, cystic spaces and lymph nodes with a malignant pattern) had a positive predictive value of 100% for malignant or borderline GISTs. In the present study, EUS evaluation showed anechoic spaces and irregular tumor margins in two patients, and surgical procedure was performed with a suspicion of malignancy. Histopathological examination confirmed the diagnosis of malignant GISTs in both of the patients.

Gastrointestinal stromal tumors usually have a normal surface mucosa, but ulceration may be seen on the surface, suggesting malignancy (19). In this study, in one of the two cases with histologically proven malignant GIST, ulceration was present on the tumor on endoscopy. However, ulceration was detected on endoscopy in all patients with upper GI bleeding. None of the operated patients with bleeding showed histopathological findings of malignancy.

Most GISTs are asymptomatic, and when symptomatic, the most common clinical presentation is gastrointestinal bleeding (20). Concordant with the literature, in this study, upper GI endoscopy was performed for nonspecific GI system symptoms, particularly dyspepsia, in 19 (76%) of the patients. Four (16%) patients were admitted with upper GI system bleeding and two (8%) patients with GIST located at the esophagus suffered from dysphagia. The localization of the GISTs and demographic properties of our patients were also consistent with the literature.

Gastrointestinal stromal tumors are usually positive for c-kit (CD117), often positive for CD34, sometimes positive for smooth muscle actin and usually negative for desmin (1, 8). It is clear that immunohistochemical stains are very important in the differential diagnosis of GISTs from other submucosal lesions, when the tumor is operated. On the other hand, some GISTs do not require operation and follow-up without treatment is recommended, unless they show malignant criteria or severe gastrointestinal bleeding is present. Thus, multiple investigators have attempted to use EUS guidance to obtain diagnostic histological material (21-24). Unfortunately, fine needle aspiration of these lesions has not been very successful. Firstly, because they are very firm, a great degree of force is required to penetrate the neoplasm with a narrow gauge needle. Secondly, the neoplasms may

be fibrotic, and it may be difficult to obtain cytological material by aspiration.

In conclusion, differential diagnosis of GISTs from the other submucosal tumors is very important. EUS evaluation is very useful in the differential diagnosis since typical EUS features of GISTs are well defined. These EUS features will usually be enough for clinicians to select the correct therapeutic method, such as operation or follow-up without treatment. EUS evaluation can also help establish whether a GIST is malignant or benign. However, for the latter, studies are still few, and the accuracy of EUS in distinguishing between malignant and benign GISTs remains to be confirmed.

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