Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours

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Abstract

Background/Aim—Some endoscopic ultrasonographic (EUS) features have been reported to be suggestive of malignancy in gastrointestinal stromal cell tumours (SCTs). The aim of this study was to assess the predictive value of these features for malignancy.

Methods—A total of 56 histologically proven cases of SCT studied by EUS between 1989 and 1996 were reviewed. There were 42 gastric tumours, 12 oesophageal tumours, and two rectal tumours. The tumours were divided into two groups: (a) benign SCT, comprising benign leiomyoma (n = 34); (b) malignant or borderline SCT (n = 22), comprising leiomyosarcoma (n = 9), leiomyoblastoma (n = 9), and leiomyoma of uncertain malignant potential (n = 4). The main EUS features recorded were tumour size, ulceration, echo pattern, cystic spaces, extraluminal margins, and lymph nodes with a malignant pattern. The two groups were compared by univariate and multivariate analysis.

Results—Irregular extraluminal margins, cystic spaces, and lymph nodes with a malignant pattern were most predictive of malignant or borderline SCT. Pairwise combinations of the three features had a specificity and positive predictive value of 100% for malignant or borderline SCT, but a sensitivity of only 23%. The presence of at least one of these three criteria had 91% sensitivity, 88% specificity, and 83% predictive positive value. In multivariate analysis, cystic spaces and irregular margins were the only two features independently predictive of malignant potential. The features most predictive of benign SCTs were regular margins, tumour size ≤ 30 mm, and a homogeneous echo pattern. When the three features were combined, histology confirmed a benign SCT in all cases.

Conclusions—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 gastrointestinal SCT. Tumours less than 30 mm in diameter with regular margins and a homogeneous echo pattern are usually benign.

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Keywords: gastrointestinal; stromal cell tumours; endoscopic ultrasonography; leiomyoma; leiomyoblastoma; leiomyosarcoma

Stromal cell tumours (SCTs) are the most common tumours of the oesophagogastric submucosa.^{1,2} Most gastrointestinal SCTs are asymptomatic and benign, but around 15% are malignant.¹⁻³

Endoscopic ultrasonography (EUS) is the most appropriate technique for studying tumours of the oesophagogastric submucosa. EUS diagnosis of SCT is based on a hypoechoic mass contiguous with the fourth hypoechoic layer (muscularis propria) or the second hypoechoic layer (muscularis mucosae) of the normal wall.^{4,5} Several authors have reported that certain EUS features of SCTs may be predictive of malignancy.^{3,6} However, the studies were small and/or multicentre series, and the ability of EUS to distinguish between benign and malignant SCTs remained to be confirmed.

The aim of this study was therefore to identify EUS features distinguishing benign from malignant gastrointestinal SCTs in a large single centre population.

Patients and methods

From March 1989 to December 1997, the files of all patients with histologically proven leiomyoma, leiomyoblastoma, or leiomyosarcoma who underwent EUS examination in our endoscopic unit were reviewed. There were 56 patients (22 men and 34 women), with a mean age of 61 years (range 28-92). There were 42 gastric tumours, 12 oesophageal tumours, and two rectal tumours. The histological specimens were obtained by surgical resection in 50 cases (89%), by endoscopic resection in three cases (5.5%), and by endoscopic or surgical biopsy in three cases (5.5%). Thirty eight leiomyomas, nine leiomyoblastomas, and nine leiomyosarcomas were diagnosed. Of the 38 leiomyomas, 34 were considered benign. Four were considered to be of indeterminate malignancy (borderline tumours), because of mitotic activity or pronounced pleomorphism and dense cellularity.^{1,2}

A total of 54 of 56 patients had undergone an upper gastrointestinal endoscopy and two a rectosigmoidoscopy with biopsies of the submucosal tumour some days or weeks before EUS. The EUS examinations were performed

Abbreviations used in this paper: EUS, endoscopic ultrasonography; SCT, stromal cell tumour.

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Table 1 Comparison of endoscopic ultrasonographic (EUS) features in benign stromal cell tumours (SCTs) and SCTs with malignant potential (univariate analysis)

Features	Borderline SCTs (n=13)	Leiomyosarcomas (n=9)	SCTs with malignant potential (borderline tumours + leiomyosarcoma) (n=22)	Benign leiomyomas (n=34)	SCTs with malignant potential versus benign leiomyomas (p value)
Maximal diameter >30 mm	10 (77)	7 (78)	17 (77)	14 (41)	0.003
Ulceration	5 (38)	7 (78)	12 (54)	10 (29)	0.06
Lymph nodes	1 (8)	4 (44)	5 (23)	1 (3)	0.02
Heterogeneity with cystic spaces	6 (46)	3 (33)	9 (41)	2 (6)	0.001
Heterogeneity without cystic spaces	3 (23)	3 (33)	6 (27)	11 (32)	0.9
Exophytic development	6 (46)	2 (22)	8 (36)	4 (12)	0.03
Extraluminal irregular margins	6 (46)	5 (56)	11 (50)	2 (6)	0.0002

Values in parentheses are percentages.

after upper gastrointestinal endoscopy (Olympus XV-100 or GIF-100) without biopsies (except for four patients) in a single institution using instruments with radial transducers of 7.5 and 12 MHZ (Olympus GF-UM 3 or GF-UM 20) (Scop Medecine Olympus, Rungis, France). All examinations were performed under intravenous sedation (midazolam with or without propofol).

The endoscopic and EUS charts, EUS photographs (n = 23), or videotapes when available (n = 33) were reviewed by one of us (LP) blinded to the final diagnosis. The following EUS features were recorded for all tumours: (a) maximal diameter; (b) presence of deep ulceration on endoscopy and/or EUS; (c) echogenicity (hypoechoic or hyperechoic); (d) heterogeneity (homogeneous *v* heterogeneous); (e) presence of cystic spaces (anechoic cavities with posterior enhancement); (f) regularity of the extraluminal border (regular *v* irregular); (g) exophytic development (bulk of tumour development outside the intestinal wall); (h) lymph nodes with malignant patterns (spherical, hypoechoic, sharply demarcated, largest diameter >1 cm).

To identify EUS features predictive of malignancy, the tumours were divided into two groups: A (n = 34), benign SCTs—that is, benign leiomyomas; B (n = 22), malignant SCTs—that is, leiomyosarcomas (n = 9)—and SCTs of uncertain malignant potential (n = 13). SCTs of uncertain malignant potential corresponded to the nine leiomyoblastomas and four leiomyomas for which a benign nature could not be determined on the pathological specimens.

STATISTICAL ANALYSIS

The EUS features were compared between group A and group B. Univariate analyses using the χ^2 test were performed to identify EUS features associated with potential malignancy with the Statview IV statistical package. Maximal diameter of the tumour was considered to be a qualitative datum (more or less than 30 mm). Multivariate logistic regression was performed to identify independent predictors of potential malignancy (JMP statistical package). p values of 0.05 or less were considered statistically significant. Calculation of sensitivity, specificity, and negative and positive predictive values of each EUS feature and combination of these features for predicting potential malignancy were carried out manually. The same calculation of sensitivity,

Figure 1 Gastric leiomyosarcoma (diameter 5 cm) with several cystic spaces (arrows).

specificity, and negative and positive predictive values was performed for predicting the benignity of the tumour.

Results

ENDOSCOPIC AND EUS FEATURES

Table 1 shows the main EUS features of the tumours.

Leiomyosarcomas (n = 9)

Leiomyosarcomas were located in the oesophagus in one patient (11%; accounting for 8% of oesophageal SCTs), in the stomach in six (67%; 14% of gastric SCT), and in the rectum in two (22%; all cases of rectal SCT). The mean maximal tumour diameter was 60 (range 26–100) mm. The tumour was ulcerated in seven cases (77%).

The tumours arose from the fourth echo poor layer in eight cases; EUS showed that one oesophageal tumour disrupted all the wall layers. Cystic spaces (fig 1) and irregular tumour margins (figs 2 and 3) were observed in three and five cases respectively (56%). The tumour echostructure and margins were homogeneous and regular in three cases each (33%), but only one patient had a homogeneous tumour with regular margins. In this latter case the tumour measured 40 mm in diameter. Involved satellite lymph nodes were present in four patients (44%), and were large nodes located in the coeliac or hepatic area in two cases; they were diagnosed by transabdominal ultrasonography before the gastric tumour was found. At least one of the following features was present in eight of nine leiomyosarcomas (89%): irregular margins, cystic spaces, lymph nodes with malignant patterns.

Benign leiomyomas (n = 34)

Benign leiomyomas were located in the oesophagus in 11 patients (32%; 92% of

Figure 2 Small gastric leiomyosarcoma (diameter 2 cm) with irregular margins (arrows)

Figure 3 The same lesion as in fig 2. Note the lateral involvement of the submucosa (arrowheads).

oesophageal SCTs) and in the stomach in 23 (68%; 55% of gastric SCTs). The mean maximal diameter of the tumour was 34 (range 8–75) mm. Ten tumours (29%) were ulcerated.

These tumours arose from or within the fourth echo poor layer in most cases ($n = 29$; 87%). Only five tumours (13%) arose from the second echo poor layer, and all five were leiomyomas of the muscularis mucosae. The echostructure was homogeneous in 58% of cases, and 60% of the 20 tumours measured less than 30 mm in diameter. One or several cystic spaces were observed in two benign leiomyomas (6%) measuring 40 and 60 mm. These spaces corresponded to cystic degeneration in one case, as shown by histological examination. In the other case, major intratumoural oedema was observed on the pathological specimen, without necrosis or cystic degeneration. Hyperechoic spots, corresponding histologically to calcifications, were observed in three cases (8%). Tumour margins were irregular in two leiomyomas (6%) measuring 25 and 35 mm. Lymph nodes with a malignant pattern were present in one case of gastric leiomyoma located at the greater curve. They were not adjacent to the tumour but had a metastatic pattern. In fact, they were metastatic lymph nodes from a colon cancer discovered during laparotomy.

Borderline tumours: leiomyoblastomas ($n = 9$) and leiomyomas ($n = 4$)

SCTs of uncertain malignancy always corresponded to gastric tumours. The mean maximal diameter of the tumour was 49 (range 30–100) mm. Five tumours were ulcerated (38%).

All the leiomyoblastomas arose from the fourth echo poor layer, with frequent extragas-

Figure 4 Gastric leiomyoblastoma (diameter 4 cm) with cystic spaces (arrowheads).

Figure 5 Gastric leiomyoblastoma (diameter 3 cm) with irregular margins (arrow).

tric development (36%). Their echostructure was often heterogeneous (67%), with cystic spaces in five cases (56%) (fig 4). The tumour margin was irregular in four cases (44%) (fig 5). No suspect lymph nodes were observed. Cystic spaces were present or the margins were irregular in eight of nine leiomyoblastomas.

All four leiomyomas for which a benign nature could not be confirmed on the pathological specimen measured more than 30 mm, while the extraluminal margins were irregular in two cases and a heterogeneous pattern without cystic spaces was found in two cases. In one case cystic spaces and a single satellite lymph node with a malignant pattern were observed. A large area of necrosis was found in the tumour on pathological examination. The lymph node corresponded to a large inflammatory node adjacent to the ulcerated necrotic tumour.

STATISTICAL ANALYSIS

Univariate analysis showed that extraluminal irregular margins, cystic spaces, a diameter greater than 30 mm, exophytic development, and lymph nodes with a malignant pattern were associated with potential malignancy (table 1). Extraluminal irregular margins ($p = 0.002$) and cystic spaces in the tumour ($p = 0.001$) were the two EUS features independently predictive of potential malignancy in logistic regression analysis ($R^2 = 0.6$).

Table 2 shows the value of each EUS feature in predicting potential malignancy. The most predictive features were irregular margins, cystic spaces, and lymph nodes with a malignant pattern. Each criterion had a high positive predictive value but limited sensitivity. The presence of two of these three features in a

Table 2 Sensitivity, specificity, and negative and positive predictive values of endoscopic ultrasonographic (EUS) features for potential malignancy—that is, leiomyosarcomas or stromal cell tumours of uncertain malignant potential

EUS features	Sensitivity	Specificity	Predictive positive value	Predictive negative value
Extraluminal irregular margins	50	91	80	76
Cystic spaces	41	94	82	71
Lymph nodes	23	97	83	66
Exophytic development	36	88	67	68
Maximal diameter >30 mm	77	59	56	83
Ulceration	54	70	54	70
Heterogeneity (without cystic spaces)	27	67	39	61

Values are expressed as percentages.

Table 3 Frequency of at least one of the three most predictive features of potential malignancy (namely irregular margins, cystic spaces, and lymph nodes) in different types of stromal cell tumours

Presence of at least one of the predictive features in:	Benign leiomyomas	Tumours of uncertain malignant potential*	Leiomyosarcomas
All tumours	4/34 (12)	12/13 (92)	8/9 (89)
Tumours ≤30 mm in diameter	2/20 (10)	3/3	2/2

Values in parentheses are percentages.

*Leiomyoblastomas and leiomyomas whose benignity could not be confirmed on the pathological specimen.

Table 4 Sensitivity, specificity, and negative and positive predictive values of endoscopic ultrasonographic (EUS) features for benignity of gastrointestinal stromal cell tumours

EUS features	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Regular margins	89	69	81	69
Diameter ≤30 mm	53	70	80	40
Homogeneous pattern	58	64	78	41

Values are expressed as percentages.

given tumour had a positive predictive value and specificity of 100% for potential malignancy, but only 23% sensitivity.

The presence of at least one of these three criteria had a sensitivity of 91%, a specificity of 88%, a positive predictive value of 83%, and a negative predictive value of 94% for potential malignancy. Some 12% of benign leiomyomas presented one of these three features. At least one of these criteria was present in all malignant SCTs and in all SCTs of uncertain malignant potential measuring less than 30 mm in diameter (table 3).

In contrast, the three features most predictive of benignity were regular margins, diameter ≤30 mm, and a homogeneous pattern (table 4). The combination of these three criteria had a sensitivity of 37% and a specificity and positive predictive value of 100% for benign SCTs.

Discussion

Gastrointestinal stromal cell tumours are often asymptomatic, usually being discovered incidentally during upper gastrointestinal endoscopy for unrelated conditions. Larger tumours may cause bleeding, abdominal pain, or obstruction. Before the advent of EUS, the management of SCTs was based on the estimated size of the tumour and the presence of manifestations attributable to the tumour.⁷ A presumptive diagnosis of SCT can now be made by using EUS.^{8–10} It is controversial whether gastrointestinal SCTs in asymptomatic patients should be removed to prevent complications or malignancy.

Histological assessment of malignancy in gastrointestinal SCTs is notoriously difficult, except in the case of invasion of adjacent structures or metastasis.^{1,2} The value of conventional histological signs such as dense cellularity and pleomorphism is controversial. The most useful variable is mitotic activity, but several grading systems are used.^{1,2,11} The prognosis of gastric leiomyoblastomas is unclear.¹² The reported rate of metastatic spread is between 3% and 38%.¹² The main problem in the asymptomatic patient is to determine whether or not the SCT has malignant potential, and this is not always shown by histological analysis. In this study we individualised SCTs of uncertain malignant potential, which pathologists classify as a subgroup of tumours.^{1,2}

Reviews of SCT studies by EUS reported until 1992 showed that certain features were suggestive of malignancy (larger non-homogeneous tumours with irregular outer margins). However, EUS was not considered a reliable tool for differentiating between benign and malignant SCTs.^{4,9} More recently, two studies showed the usefulness of EUS in this indication.^{3,6} In contrast, the accuracy of endosonography guided fine needle aspiration biopsy is limited in gastrointestinal wall lesions.¹³ Yamada *et al*⁶ reported five EUS features predictive of malignancy: tumour diameter ≥30 mm, nodular shape, depth of ulceration (≥5 mm), a heterogeneous pattern, and the presence of cystic spaces; however, the series included only four malignant tumours. Chak *et al*³ recently reported that four EUS features were helpful in predicting SCT malignancy, comprising size, irregular extraluminal borders, cystic spaces (greater than 4 mm), and echogenic foci (greater than 3 mm). Agreement on these features between observers was only fair to moderate, and was poor for irregular luminal borders.

We analysed the eight EUS features commonly recorded in our institution. Only irregular extraluminal margins and cystic spaces were independent predictors of potential malignancy. Tumour size is a reliable predictor of malignant potential.¹⁴ Moreover, in gastrointestinal leiomyosarcomas, larger lesions have a greater tendency than smaller ones to metastasise,¹⁴ but the large degree of size overlap rules out the use of this parameter alone to predict malignancy.^{1,2} In our series the mean size of benign leiomyomas was relatively large, as only histologically defined tumours were studied. This size was not representative of benign SCTs, as in our experience most asymptomatic patients with small tumours did not receive surgery. Most tumours project into the gastric lumen as polypoid submucosal growths and are prone to surface ulceration. Some SCTs protrude from the outer surface as exophytic subserosal lesions, while a few may grow in both directions to produce a dumb bell appearance. Exophytic development and ulceration are more common in larger tumours.¹ The low incidence of lymph node metastases of gastrointestinal leiomyosarcomas is well known. A review of published series gave nodal metastasis rates of 7–13%.^{14,15} Our patient

sample did not mirror this frequency, as four of the nine leiomyosarcomas (44%) were associated with nodal metastases, but two of these patients had large nodal metastases which led to the discovery of the gastric leiomyosarcoma and probably accounted for this difference.

A combination of three criteria (regular extraluminal margins, diameter ≤ 30 mm, and homogeneous pattern) had a sensitivity of 37% and a specificity and predictive positive value of 100% for benignity. In patients with such features, EUS may be a useful decision aid, particularly if they are at an increased risk of surgery or have lesions that are difficult to resect—for example, oesophageal tumours. However, this approach needs to be validated in a prospective study.

As in other such studies, our results should be interpreted in the light of technical limitations.³ Firstly, this was a retrospective study. Videotapes were not available for all the patients, as they were not recorded when lesions were small and had no EUS features of malignancy. Secondly, although EUS was performed in a single institution, patients came from several centres and were selected for surgery according to institutional criteria. Thirdly, the histological specimens were not all reviewed by the same pathologist. It should be noted, however, that the leiomyosarcomas and SCTs of uncertain malignancy had already been reviewed by referral pathologists from different university hospitals.

In conclusion, EUS is reliable in predicting the potential malignancy of SCTs. The three most predictive EUS features are irregular margins, cystic spaces, and lymph nodes with a malignant pattern. The presence of at least one of these criteria had a sensitivity of 91%, a specificity of 88%, a positive predictive value of 83%, and a negative predictive value of 94% for potential malignancy. A combination of two of

these three criteria had a positive predictive value and specificity of 100%. In contrast, tumours of 30 mm or less, with regular extraluminal margins and a homogeneous pattern, are likely to be benign.

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