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ORIGINAL ARTICLE

Suggested cutoff tumor size for management of small EUS-suspected gastric gastrointestinal stromal tumors

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Background/Purpose: Although the incidence of asymptomatic small gastric submucosal tumors increased gradually with routine medical health examination, there was little clinical evidence for management consensus in these small gastric submucosal tumors including endoscopic ultrasound (EUS)-suspected gastric gastrointestinal stromal tumors (GISTs). We investigated the clinical course of small EUS-suspected gastric GISTs and propose a cutoff value of tumor size for treatment policy.
Methods: In this retrospective study, 50 patients with EUS-suspected gastric GISTs of sizes less than 3 cm were enrolled and were followed up by EUS at least twice over a period of more than 24 months (range 24–101 months). An at least 20% increase of the maximal diameter of the tumors was set as a significant change.
Results: Significant changes in tumor size were found during the follow-up in 14 patients (28.0%). The one-dimensional 20% change corresponded well to 50% change in two-dimensional area measurement (correlation coefficient = 0.929). The receiver operating characteristic curve analysis showed that the best cutoff size, associated with tumor progression, was 1.4 cm having an 85.7% sensitivity, 86.1% specificity, and 86.0% accuracy. A larger tumor

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size (35.7% vs. 2.8%, $p = 0.005$) and irregular tumor margin on the EUS (71.4% vs. 0, $p = 0.004$) were two significant factors associated with the progression of tumor growth of small suspected gastric GISTs.
Conclusion: Small EUS-suspected GISTs, larger than 1.4 cm, with irregular margin were associated with significant progression. This subgroup is suggested to be monitored by more intensive follow-up.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common submucosal tumors (SMTs) found in the stomach.[1] Because clinical symptoms are usually nonspecific, the true incidence of either gastric GISTs or other gastric SMTs remains unclear. Most such lesions are incidentally found during routine endoscopic examination or at autopsy. One previous study estimated the incidence of gastric SMTs to be 0.36% by endoscopic diagnosis.[2] However, several studies have suggested an incidence of gastric GISTs between 10 and 20 cases per million based on surgical and autopsy specimens.[3–5]

Endoscopic ultrasound (EUS) has been used for the evaluation of the SMTs of the stomach with a high accuracy.[6–13] The typical EUS finding of a gastric GIST is a hypoechoic lesion arising from the fourth layer of the gastric wall. The diagnostic accuracy of gastric GISTs by EUS alone (by experienced endoscopists) is as high as 87%.[13–15] Several studies have proposed EUS characteristics for predicting the malignant potential of GISTs, including a larger size (more than 3 cm), heterogeneous echogenicity, irregular borders, cystic changes, calcification, exogastric growth, echogenic foci, lobulation, and ulceration.[11,13,16,17]

Surgical intervention is the treatment of choice for gastric GISTs larger than 2 cm, while conservative follow-up is suggested for lesions less than 2 cm.[18–20] EUS-guided fine-needle aspiration (EUS-FNA), to exclude a malignancy, was recommended for gastric GISTs of sizes between 2 and 5 cm.[21,22] However, little is known about the natural course of small EUS-suspected gastric GISTs. This makes the decisions on interventions for smaller gastric GISTs difficult.

The tumor growth potential is an important index of malignancy.[23] The goal of this study was to evaluate the natural course of small EUS-suspected gastric GISTs less than 3 cm, a subgroup with consistent EUS features of GISTs, but usually lacking histological confirmation at initial diagnosis. The best cutoff size was determined for the prediction of significant tumor growth. This would provide clinicians with information needed for appropriate intervention.

Methods

Study design and population

We retrospectively reviewed patients with a diagnosis of suspected gastric GISTs by EUS at the National Taiwan University Hospital, Yuan's General Hospital, and En Chu Kong Hospital from January 1997 to December 2008.

An EUS-suspected gastric GIST was defined as a hypoechoic lesion arising from the fourth layer of the gastric wall shown on EUS. Written informed consents were obtained from all patients before EUS studies. Miniprobes (Olympus UM-2R, 12 MHz or UM-DP12-25R, 12 MHz; Olympus, Tokyo, Japan) were used for the EUS examinations in this study. All EUS images and video files were reviewed by three experienced EUS endoscopists (HP Wang, MS Sun, and CS Yang).

Four criteria were required for study enrollment: (1) a small tumor size, less than 3 cm, without definite EUS characteristics of malignancy such as extragastric growth and lobulation; (2) patients declining surgical intervention at initial identification of the lesions; (3) EUS follow-up frequency of at least two times; (4) EUS follow-up period of more than 24 months.

Study procedures and assessments

All clinical data and EUS characteristics were reviewed for subsequent analysis. Patients with EUS-suspected GISTs, less than 3 cm, were enrolled and followed up. The natural course of tumor growth was evaluated by EUS. We set an increase of at least 20% in the maximal diameter of the tumors as progressive disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Patients were classified as the tumor-progressive subgroup when a significant change in tumor size was noted or as the tumor-stationary subgroup when no change was observed. All two-dimensional (2D) measurements were assessed using the image processing software ImageJ 1.41e (NIH, USA).[24]

This study was conducted in accordance with National Taiwan University Hospital research protocol, and was approved by the Human Subjects Research Ethics Committee of the National Taiwan University Hospital.

Statistical analysis

All statistical analyses were carried out with statistical software (SPSS version 10.0 for Windows; SPSS, Chicago, IL, USA). The sensitivity and specificity of various tumor sizes were analyzed using the receiver operating characteristic (ROC) curve, and the best cutoff value was determined. The relationship between the study parameters and the tumor size were analyzed using the Pearson chi-square test. Statistical significance was set at the standard 5% level.

Results

Characteristics of patients and tumors

Fifty patients meeting the criteria for the diagnosis of EUS-suspected GISTs were enrolled. The average initial tumor size was 1.1 cm (range 0.4—3.0 cm). The mean EUS follow-up period was 39.2 months (range 24—101 months). The mean EUS follow-up frequency was 3.2 (range 2—9 times). No significant change in echo patterns was observed in 41 patients (82.0%). Seven patients had undergone surgical resection, and all their tumors proved to be GISTs.

With consideration of tumor progression, significant change in tumor size was found in 14 patients (28.0%) during the follow-up. Four of these 14 patients underwent surgery, while the other 10 patients refused surgery and were followed up regularly (at least once a year) for an average of 51.2 months (range 33—101 months). Two of the four patients undergoing surgery had lesions with high malignant potential, reflected by mitotic rates of more than 10 per 50 high-power fields (HPFs).

Demography of the 50 patients and various parameters of small EUS-suspected GISTs are shown in Table 1. The average tumor growth rate in this progressive disease group was 17.1% per year, which was significantly higher than 1.0% per year in the stationary disease group (Fig. 1).

Table 1 Demography and various parameters of small EUS-suspected GISTs in 50 patients.

Parameter	Stationary disease ($n = 36$)	Progressive disease ($n = 14$)	p
Age (yr)			
≦65	29	8	0.149
>65	7	6	
Gender			
Male	12	7	0.276
Female	24	7	
Symptom			
Asymptomatic	34	11	0.126
Symptomatic	2	3	
Comorbidity			
Present	7	1	0.414
Absent	29	13	
Initial size (cm)			
<2	35	9	0.005
≧2	1	5	
Location			
Cardia to upper body	30	11	0.697
Middle body to antrum	6	3	
Echogenicity			
Homogeneous	34	11	0.126
Heterogeneous	2	3	
Tumor margin			
Regular/smooth	36	10	0.004
Irregular	0	4	

ROC curve evaluation

With the 2 cm cutoff, the lowest limit for resection currently accepted, tumors of larger sizes would be significantly associated with tumor progression (35.7% vs. 2.8%, $p = 0.005$). Only one case with a tumor size of 2 cm remained in the stationary size after 39 months of follow-up. Since there was significant proportion of cases with a tumor size smaller than 2 cm in the tumor progression group, we performed an ROC curve analysis to determine the best cutoff size for the prediction of potential tumor growth (Fig. 2). We found 1.4 cm to be the best cutoff tumor size associated with tumor progression, with a sensitivity of 85.7%, specificity of 86.1%, positive predictive value of 70.6%, negative predictive value of 93.9%, and an accuracy of 86.0%.

Among the seven patients who underwent operation, five patients had an initial tumor size larger than 1.4 cm, and two of them (40%) belonged to the high risk group (mitosis >10/50 HPFs). The other two patents with initial tumor size smaller than 1.4 cm belonged to the very low risk group (mitosis <5/50 HPFs).

Correlation between 1D and 2D evaluation

All EUS lesions were analyzed for 2D assessment with image processing software ImageJ. The last EUS lesion during follow-up was compared to the initial EUS lesion (Fig. 3). A good linear relationship was shown during comparison between percentage changes of 1D and 2D measurements (Fig. 4). The 1D 20% change corresponded well to

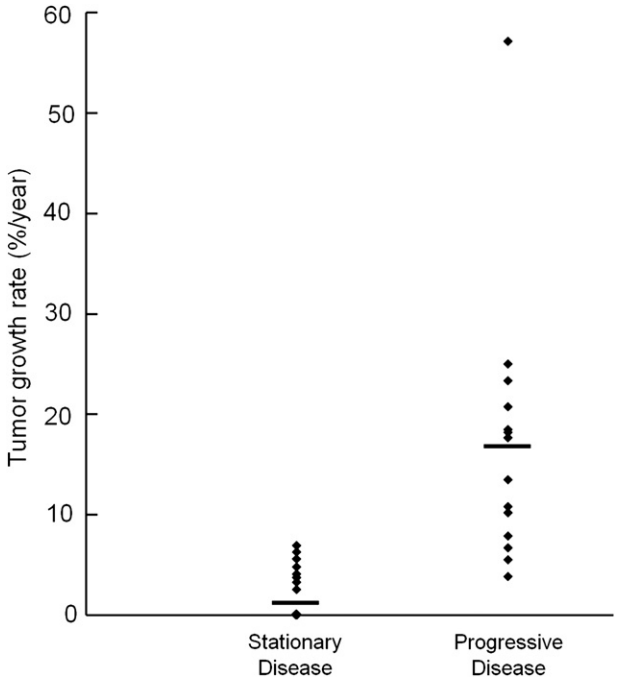
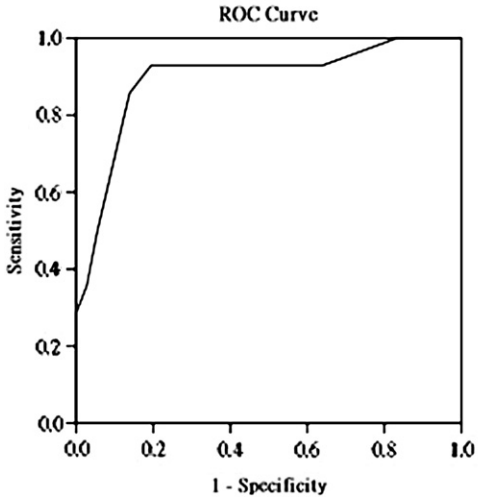


Figure 1 The average tumor growth rate in this progressive disease group was significantly higher than that in the stationary disease group.



Positive if ≥ (cm)	Sensitivity	Specificity
0.5	1.000	0.028
0.6	1.000	0.167
0.7	0.929	0.361
0.8	0.929	0.444
0.9	0.929	0.556
1.0	0.929	0.667
1.1	0.929	0.778
1.2	0.929	0.806
1.4	0.857	0.861
1.6	0.500	0.944
1.8	0.357	0.942
2.1	0.286	1.000
2.2	0.214	1.000
2.4	0.143	1.000
2.8	0.071	1.000
4.0	0.000	1.000

Figure 2 Receiver operating characteristic curve was plotted with coordinates derived from various cutoff values.

approximately 50% change in 2D area measurement (correlation coefficient = 0.929).

Risk factor analysis

The chi-square test was used to compare the parameters of patients in the tumor-stationary group with those in the tumor-progressive group. There were no significant differences observed with regard to age, gender, symptoms, comorbidity, tumor location, and EUS echogenicity. Patients in the tumor-progressive group had a higher proportion of lesions with irregular tumor margin (Fig. 5) on the EUS compared with patients in the tumor-stationary group (71.4% vs. 0%, $p = 0.004$).

After ROC curve analysis showed 1.4 cm to be the best cutoff tumor size associated with tumor progression, we performed the chi-square test again to confirm the association of tumor size with tumor growth between smaller and larger tumors. Larger tumors at least 1.4 cm in size were at increased risk for tumor growth (70.6% vs. 6.1%, $p<0.001$) and symptomatic presentation (23.5% vs. 3.0%, $p = 0.022$), and characterized with irregular tumor margins (23.5% vs. 3.0%, $p = 0.022$).

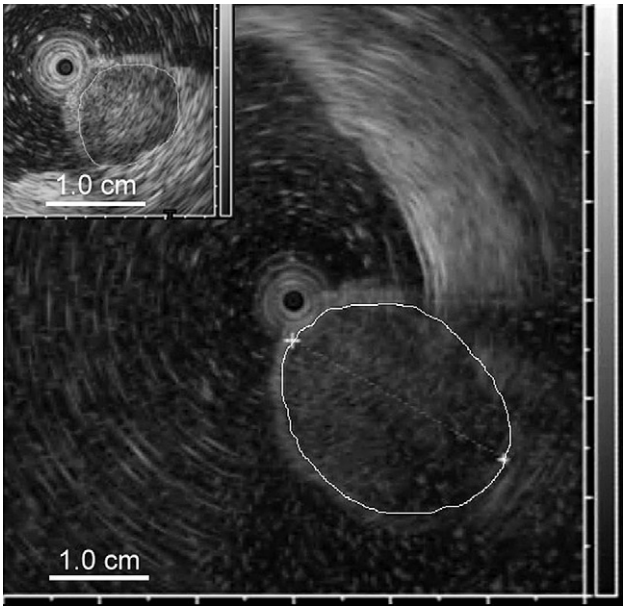


Figure 3 The last endoscopic ultrasound (EUS) picture of one patient during follow-up was compared to the initial EUS lesion (left upper insert) with aid of ImageJ software for both one-dimensional (1D) and 2D measurements.

Discussion

GISTs are known to be the most common mesenchymal neoplasm of the gastrointestinal tract. The stomach

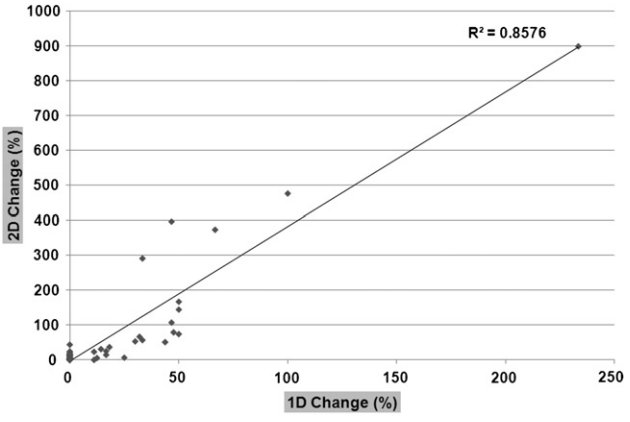


Figure 4 Good linear relationship was illustrated on comparing percentage changes of 1D and 2D measurements.

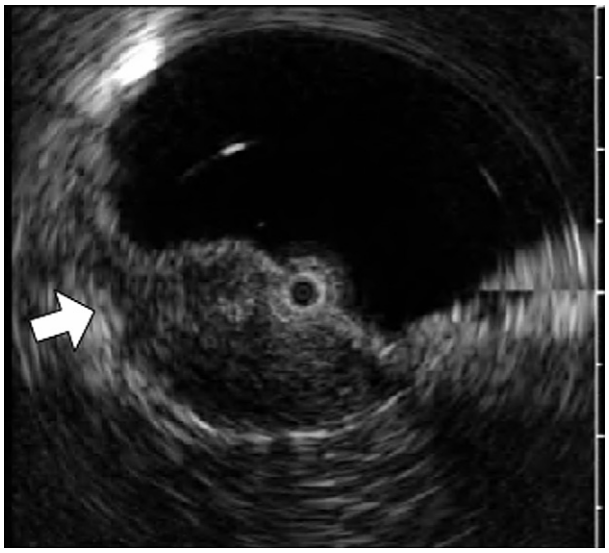


Figure 5 EUS showed a small gastrointestinal stromal tumor with irregular margin (arrow).

(50—60%) and the small bowel (25—30%) are the most common sites of GISTs.[1,25,26] Despite the success of imatinib mesylate in the treatment of advanced GISTs, surgical resection is still the treatment of choice for patients with primary GISTs without evidence of metastases. Several risk factors have been identified for predicting the aggressive behavior of GISTs. Tumor size and mitotic activity were two most well-documented factors in the National Institutes of Health consensus.[27] In addition, tumor location plays an important role.[28] Small bowel GISTs has higher progression rates than gastric GISTs of similar tumor size and mitotic activity.[29]

Because the natural course of small GISTs remains largely unknown, the current management policy for gastric GISTs less than 2 cm is usually conservative, unless tumors grow or symptoms occur. EUS-guided FNA for the determination of malignant potential has been suggested for gastric GISTs with the size of 2—5 cm.[22] The diagnostic sensitivity, specificity, and accuracy of EUS-FNA have been reported to be 66.7%, 100%, and 91.7%, respectively.[21] However, it would be difficult to use EUS-FNA for all gastric GISTs less than 2 cm from both technical and cost-effective points of view.[22] It should be noted though that a more thorough and effective interventional strategy is needed for small isolated gastric GISTs found incidentally on endoscopy.

In this study, we evaluated the tumor characteristics of small gastric GISTs, less than 3 cm, identified by EUS. Among the 50 cases enrolled in this study, we evaluated the association of the initial tumor size with tumor progression. Most cases with a tumor size of at least 2 cm had a significant progression of tumor growth. However, the widely accepted "2 cm criteria" was not adequate for separating the progressive tumors from the stationary ones in our study. The ROC curve analysis identified 1.4 cm as the best predictor of tumor progression with a good sensitivity (85.7%), specificity (86.1%), and accuracy (86.0%). Further confirmation of these findings is needed in a larger multicenter cohort. Our results are similar with those found in the study conducted in Israel, which stated that GISTs larger than 17 mm at initial diagnosis had potential enlargement.[30] However, our data were specific for GISTs of the stomach, and our mean initial tumor size (average 11.1 mm) was smaller than that used in the Israel study (average 20.5 mm). We adopted 1D assessment in this study for its convenience in clinical practice, and this simplification was in accordance with the idea of widely accepted RECIST guidelines in the evaluation of tumor size.[31] We confirmed this 1D simplification to be as effective as 2D measurement after linear correlation with image processing software ImageJ.

In this study, we used EUS as the major imaging procedure for monitoring tumor status. The EUS has previously been identified as the most accurate tool for evaluating gastric SMTs including GISTs.[6—8] Previous studies have proposed EUS characteristics associated with malignant GISTs: larger size (more than 3 cm), heterogeneous echogenicity, irregular borders, the presence of cystic changes, calcifications, exogastric growth, echogenic foci, lobulation, and ulceration.[11,13,16,17] Our findings were consistent with these prior results and suggested that irregular tumor margins were as important as tumor size in predicting tumor progression in small gastric GISTs. However, we could not confirm the significance of other EUS patterns between the progressive and stationary groups of small EUS-suspected gastric GISTs in our study.

The symptoms on presentation of the gastric GISTs were usually nonspecific and depended on the size of lesions. Symptoms associated with mass effects and bleeding were the most common clinical presentations. One previous report had estimated that the mean size of a symptomatic tumor was 6.0 cm compared to the 2.0 cm size of tumors found incidentally and the 0.5 cm size of those found at autopsy.[3] In one recent study, presentation with symptom was associated with a poor 5-year disease-free survival (HR 2.5, $p = 0.04$).[32] In our study, the mean initial tumor size was 1.1 cm. Symptomatic tumors accounted for only 10.0% (5/50) of the patients in our series. Four patients had the symptom of epigastralgia, and only one presented tarry stool. Our results only showed a nonsignificant trend for patients with symptomatic presentations to have a progressive disease process. Further analysis between tumor size effects and symptom presentation was not possible because of the small case number in this study.

There are several limitations in this study. First, only a portion (14%) of the EUS-suspected gastric GIST group had pathological confirmation. Although previous studies showed excellent correlation of the EUS features with gastric CD117-positive GISTs,[33] pathological confirmation with immunohistochemical staining was the gold standard for a definitive diagnosis. Further studies with the aid of EUS-FNA may provide additional confirmation. Second, the resolution of the videotape images for the evaluation of echo features may not have been sharp enough at times in this retrospective review. Third, tumor size alone is not enough to predict aggressive behaviors in GISTs, but it is an easy and reproducible index in clinical practice. The current follow-up observation policy for GISTs of sizes less than 2 cm made other indexes such as mitotic count interpretation difficult to perform due to the lack of

surgically resected specimens. We have refined the tumor size criteria to a reasonable lower limit with a noninvasive approach. Longer follow-up periods could justify this refinement. Finally, there was no standard follow-up program in our study groups.

Conclusion

To sum up, small EUS-suspected GISTs larger than 1.4 cm and irregular tumor margin were associated with tumor progression and probably increased malignant potential. They should be monitored by more intensive follow-up programs. Further prospective study with longer follow-up period and EUS-FNA sampling could provide important information on the natural course of small gastric GISTs and possible treatment guidelines.

References

1. Miettinen M, Lasota J. Gastrointestinal stromal tumors (GISTs): definition, occurrence, pathology, differential diagnosis and molecular genetics. *Pol J Pathol* 2003;**54**:3—24.
2. Hedenbro JL, Ekelund M, Wetterberg P. Endoscopic diagnosis of submucosal gastric lesions. The results after routine endoscopy. *Surg Endosc* 1991;**5**:20—3.
3. Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. *Cancer* 2005;**103**:821—9.
4. Tryggvason G, Gíslason HG, Magnússon MK, Jónasson JG. Gastrointestinal stromal tumors in Iceland, 1990—2003: the Icelandic GIST study, a population-based incidence and pathologic risk stratification study. *Int J Cancer* 2005;**117**:289—93.
5. Goettsch WG, Bos SD, Breekveldt-Postma N, Casparie M, Herings RM, Hogendoorn PC. Incidence of gastrointestinal stromal tumours is underestimated: results of a nation-wide study. *Eur J Cancer* 2005;**41**:2868—72.
6. Yasuda K, Nakajima M, Yoshida S, Kiyato K, Kawai K. The diagnosis of submucosal tumors of the stomach by endoscopic ultrasonography. *Gastrointest Endosc* 1989;**35**:10—5.
7. Caletti G, Zani L, Bolondi L, Brocchi E, Rollo V, Barbara L. Endoscopic ultrasonography in the diagnosis of gastric submucosal tumor. *Gastrointest Endosc* 1989;**35**:413—8.
8. Yasuda K, Cho E, Nakajima M, Kawai K. Diagnosis of submucosal lesions of the upper gastrointestinal tract by endoscopic ultrasonography. *Gastrointest Endosc* 1990;**36**:S17—20.
9. Buscarini E, Stasi MD, Rossi S, Silva M, Giangregorio F, Adriano Z, et al. Endosonographic diagnosis of submucosal upper gastrointestinal tract lesions and large fold gastropathies by catheter ultrasound probe. *Gastrointest Endosc* 1999;**49**:184—91.
10. Hizawa K, Matsumoto T, Kouzuki T, Suekane H, Esaki M, Fujishima M. Cystic submucosal tumors in the gastrointestinal tract: endosonographic findings and endoscopic removal. *Endoscopy* 2000;**32**:712—4.
11. Rösch T, Kapfer B, Will U, Baronius W, Strobel M, Lorenz R, et al. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. *Scand J Gastroenterol* 2002;**37**:856—62.
12. Shim CS, Jung IS. Endoscopic removal of submucosal tumors: preprocedure diagnosis, technical options, and results. *Endoscopy* 2005;**37**:646—54.
13. Brand B, Oesterhelweg L, Binmoeller KF, Sriram PV, Bohnacker S, Seewald S, et al. Impact of endoscopic ultrasound for evaluation of submucosal lesions in gastrointestinal tract. *Dig Liver Dis* 2002;**34**:290—7.
14. Franquemont DW. Differentiation and risk assessment of gastrointestinal stromal tumors. *Am J Clin Pathol* 1995;**103**:41—7.
15. Chak A. EUS in submucosal tumors. *Gastrointest Endosc* 2002;**56**:S43—8.
16. Chak A, Canto MI, Rösch T, Dittler HJ, Hawes RH, Tio TL, et al. Endosonographic differentiation of benign and malignant stromal cell tumors. *Gastrointest Endosc* 1997;**45**:468—73.
17. Palazzo L, Landi B, Cellier C, Cuillerier E, Roseau G, Barbier JP. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. *Gut* 2000;**46**:88—92.
18. Lai IR, Chen CN, Lin MT, Lee PH. Surgical treatment of gastric gastrointestinal stromal tumors: analysis of 92 operated patients. *Dig Surg* 2008;**25**:208—12.
19. Demetri GD, Benjamin RS, Blanke CD, Blay JY, Casali P, Choi H, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)—update of the NCCN clinical practice guidelines. *J Natl Compr Cancer Netw* 2007;**5**:S1—29. quiz S30.
20. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY. ESMO Guidelines Working Group. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;**204**:64—7.
21. Ando N, Goto H, Niwa Y, Hirooka Y, Ohmiya N, Nagasaka T, et al. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. *Gastrointest Endosc* 2002;**55**:37—43.
22. Nishida T, Hirota S, Yanagisawa A, Sugino Y, Minami M, Yamamura Y, et al. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. *Int J Clin Oncol* 2008;**13**:416—30.
23. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;**100**:57—70.
24. Rasband WS. *ImageJ*. Bethesda, MD, USA: U.S. National Institutes of Health, http://rsb.info.nih.gov/ij/; 1997—2005.
25. Urbańczyk K, Limon J, Korobowicz E, Chosia M, Sygut J, Karcz D, et al. Gastrointestinal stromal tumors. A multicenter experience. *Pol J Pathol* 2005;**56**:51—61.
26. Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. *Lancet* 2007;**369**:1731—41.
27. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002;**33**:459—65.
28. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. *Am J Surg Pathol* 1999;**23**:82—7.
29. Tashiro T, Hasegawa T, Omatsu M, Sekine S, Shimoda T, Katai H. Gastrointestinal stromal tumour of the stomach showing lymph node metastases. *Histopathology* 2005;**47**:438—9.
30. Lachter J, Bishara N, Rahimi E, Shiller M, Cohen H, Reshef R. EUS clarifies the natural history and ideal management of GISTs. *Hepatogastroenterology* 2008;**55**:1653—6.
31. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, National cancer institute of the United States, National cancer institute of Canada. *J Natl Cancer Inst* 2000;**92**:205—16.
32. van der Zwan SM, DeMatteo RP. Gastrointestinal stromal tumor: 5 years later. *Cancer* 2005;**104**:1781—8.
33. Hassan I, You YN, Shyyan R, Dozois EJ, Smyrk TC, Okuno SH, et al. Surgically managed gastrointestinal stromal tumors: a comparative and prognostic analysis. *Ann Surg Oncol* 2008;**15**:52—9.