Int J Clin Exp Med 2016;9(5):8615-8623
www.ijcem.com /ISSN:1940-5901/IJCEM0018392

Original Article

Preoperative diagnosis and prognosis of gastric stromal tumors using endoscopic ultrasonography

Wei Ge[1], Ying Lv[2], Gang Chen[1], De-Cai Yu[1], Yi-Tao Ding[1]

[1]Department of General Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing 210008, Jiangsu Province, P. R. China; [2]Department of Digestive System, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing 210008, Jiangsu Province, P. R. China

Received August 11, 2015; Accepted March 24, 2016; Epub May 15, 2016; Published May 30, 2016

Abstract: Objective: Accurate preoperative diagnosis and prognosis of a gastric stromal tumor is vital to its effective treatment. This study aimed to evaluate the value of endoscopic ultrasonography in gastric stromal tumor diagnosis and prognosis. Methods: We retrospectively analyzed 213 cases of gastric stromal tumor diagnosed preoperatively by endoscopic ultrasonography from June 2010 to June 2014, especially endoscopic ultrasonography results, and pathological findings. Results: The common locations included stomach fundus (n = 120), gastric body (n = 65), and sinuses ventriculi (n = 28). The patients' symptoms were various. A definitive diagnosis depended on postoperative pathologic and immunohistochemical examination. The pathologic results showed that 63 of 213 cases (29.6%) were misdiagnosed by endoscopic ultrasonography. Tumor diameter, age, concurrent bleeding, and characteristics in endoscopic ultrasonography such as mucosal bridge and echo may have been the misdiagnosis factors, while lesion site, and characteristics like smooth surface, ulcer in the center, and boundary had nothing to do with misdiagnosis. Endoscopic ultrasonography characteristics including smooth surface and center ulcer were correlated with the malignant risk of gastric stromal tumor, but not uniformity echo, shape, mucosal bridge, and clear boundary. Conclusions: Endoscopic ultrasonography is a useful method to diagnose gastric stromal tumor with a misdiagnosis rate of 29.6%, and definite diagnosis relies on immunohistochemical analysis. Tumor diameter, age, concurrent bleeding, and characteristics in endoscopic ultrasonography such as mucosal bridge and echo may be misdiagnosis factors. Concurrent bleeding and endoscopic ultrasonography indexes of the smooth surface and center ulcer are potential prognostic factors of gastric stromal tumor.

Keywords: Endoscopic ultrasonography, gastric stromal tumors, GST, misdiagnosis, prognosis

Introduction

Gastric stromal tumors (GSTs) were described in 1983 as tumors in the gastrointestinal (GI) tract and mesentery, characterized by a specific histological and immunohistochemical pattern [1]. GSTs, derived from the interstitial cells of Cajal [2, 3], are now considered potentially malignant and have the risk of metastatic relapse, so all GSTs need to be resected, including even small intramural lesions of the GI tract [4, 5]. However, since not all intramural lesions of the GI tube are GSTs, an accurate preoperative diagnosis is very important. Endoscopic ultrasonography (EUS), enabling intramural scanning of the GI tract, is reportedly useful in diagnosing GST and differentiating GST from extraluminal lesions [6-10]. This study aimed to evaluate the value in EUS in GST diagnosis and prognosis. All cases underwent surgical resection.

Material and methods

We reviewed all cases in the record room files from June 2010 to June 2014 and identified 213 cases diagnosed as GST preoperatively by EUS. This study was approved by the IRB of Nanjing Drum Tower Hospital, the affiliated hospital of Nanjing University Medical School. We then reviewed the clinical and EUS data, treatment, and pathological findings of these cases. We recorded the patients' age and gender, lesion site, clinical symptoms at onset, auxiliary examination, treatment, and pathological examination.

Table 1. Clinicopathological characteristics of the patients (n = 213)

Age (years)			
< 40	19	40-60	111
> 60	83		
Gender			
Male	92	Female	121
Anatomical sites of lesions			
Fundus of stomach	120	Gastric body	65
Sinuses ventriculi	28		
Final diagnosis after EUS			
GST	150	Leiomyoma	28
Schwannoma	18	Heterotopic pancreas	6
Vascular malformation	2	Polypus	2
Cyst	2	Stomach repeat deformity	1
Ectopic spleen	1	Glomus tumor	1
Nodular fibrous pseudotumor	1	Inflammatory myofibroblastic tumor	1

GST: gastric stromal tumor.

We reviewed the findings of different auxiliary examinations including EUS (n = 213), endoscopy (n = 132), Computed Tomography (CT, n = 100), and upper gastrointestinal contrast (n = 8). We performed a histopathological examination of surgical specimens using standard hematoxylin and eosin staining (HE), as well as special immunohistochemical techniques. Immunohistochemical staining was performed using a Dako EnVision System according to the manufacturer's instructions with primary antibodies including CDII7, CD34, Smoothmuscle actin (SMA), S100 calcium binding protein (S-100), and Desmin. Diaminobenzidine was used as the chromogen. Patient managements were also recorded.

We used the student t test to compare the size and age of GSTs and non-GSTs. The misdiagnosis rates of clinical and EUS characteristics were assessed using the Chi-Square test. Associations among clinical and EUS characteristics were assessed using the Wilcoxon-Mann-Whitney test or Pearson Correlation. $P < 0.05$ was considered statistically significant. All P values were two sided. All statistical calculations were performed using SAS software (version 9.0).

Results

Baseline characteristics

There were 213 patients diagnosed as GST preoperatively by EUS (92 men and 121 women, ages ranging from 9 to 85 years, with mean age 56.6 years). The common locations were in the stomach fundus (n = 120), gastric body (n = 65), and sinuses ventriculi (n = 28) (**Table 1**). The symptoms were various, such as abdominal pain, hematemesis, melena, sour regurgitation, and belching. Some patients were diagnosed by lab examination with no discomfort, and only 26 patients complained of bleeding.

All patients underwent surgical resection with no serious complications, and there were no cases of postoperative mortality. In total, 114 patients underwent laparoscopic surgery, while 99 underwent open surgery. The definitive diagnosis was based on postoperative pathologic and immunohistochemical examinations. The results showed that 63 of 213 patients (29.6%) were misdiagnosed. These patients were proven to have the following conditions: leiomyoma in 28 patients, schwannoma in 18, heterotopic pancreas in 6, vascular malformation in 2, polypus in 2, cyst in 2, stomach repeat deformity in 1, ectopic spleen in 1, glomus tumor in 1, nodular fibrous pseudotumor in 1, and inflammatory myofibroblastic tumor in 1 patient (**Table 1**). Immunocytochemical results were integral to us reaching a definite diagnosis, as summarized in **Table 2**. For GST, CD117, CD34, and Delay of Germintion 1 (Dog1) expressions were positive in 149 (99.3%), 146 (97.3%), and 67 (98.5%) patients, respectively. For leiomyoma, SMA and Desmin were positive in 25 (100%) and 27 (100%) patients, respectively. For schwannoma, S-100 was positive in 18 (100%) patients.

EUS indexes for GST diagnosis

All mass was evaluated using EUS. We evaluated the effect of EUS indexes on diagnosing GST and divided the patients into GST and non-GST groups (**Table 3**). We analyzed the EUS indexes of the GST and non-GST groups including the smooth surface, center ulcer, mucosal bridge, shape, echo, and boundary (**Table 3**). The re-

Table 2. Cytologic interpretations and immunocytochemical findings from gastrointestinal mesenchymal neoplasms

Cytologic interpretation	CD34	CD117	SMA	Desmin	S100	Dog1
GST	146/150	149/150	37/140	7/150	16/148	67/68
Leiomyoma	4/28	3/28	25/25	27/27	4/27	0/9
Schwannoma	1/17	0/18	2/17	0/18	18/18	1/9
Heterotopic pancreas	ND	ND	ND	ND	ND	ND
Vascular malformation	ND	ND	ND	ND	ND	ND
Polypus	1/2	0/2	1/1	0/2	0/2	0/1
Cyst	ND	ND	ND	ND	ND	ND
Stomach repeat deformity	ND	ND	ND	ND	ND	ND
Ectopic spleen	ND	ND	ND	ND	ND	ND
Glomus tumor	0/1	0/1	1/1	0/1	0/1	ND
Nodular fibrous pseudotumor	0/1	0/1	0/1	0/1	0/1	ND
Inflammatory myofibroblastic tumor	0/1	0/1	1/1	1/1	0/1	ND

ND: not done, GST: gastric stromal tumor, CD: Cluster of Differentiation, SMA: Smoothmuscle actin, S100: S100 calcium binding protein, Dog1: Delay of Germintion 1. Data are given as number positive/number tested.

sults showed that misdiagnosis had no correlation with the smooth surface, center ulcer, shape, and boundary, while the mucosal bridge and echo affected the diagnosis.

The average GST diameter was larger than that of non-GSTs (4.31±3.19 vs. 2.9±1.78 cm). The patients were divided into three groups according to their tumor diameter (< 2 cm, 2-5 cm, and > 5 cm). The tumor diameter misdiagnosis rates < 2 cm, 2-5 cm, and > 5 cm were 42.20%, 31.90%, and 13.50%, respectively. The *P* value was 0.000 (**Table 3**). Age and concurrent bleeding may be misdiagnosis factors, so we created statistics of age and concurrent bleeding between GSTs and non-GSTs (**Table 3**). The results showed that the *p* values were 0.000 and 0.0378, respectively. Then we created statistics of gender (**Table 3**). We found that the *p* value was 0.5027, without statistical differences. The lesion sites were also summarized in **Table 3**, and the *p* value was 0.8946.

Mentioned above, age, tumor size, concurrent bleeding, the mucosal bridge, and uniform echo were considered misdiagnosis risk factors. The relationship between EUS indexes and tumor size was further analyzed (**Table 4**). There was no relationship between tumor size and the mucosal bridge, while uniform echo was relevant to tumor size ($P < 0.0001$).

EUS indexes associated with GST prognosis (risk of aggressive behavior)

The malignant risk of GST was stratified into categories including very low, low, moderate, and high risk according to tumor size and mitotic index identified on surgical histology. We evaluated whether EUS predicted malignant risk of GST. The results showed no statistical significance in the characteristics such as uniformity echo, shape, the mucosal bridge, and clear boundary among very low, low, moderate, and high risk groups as well as age, gender, and lesion site (**Table 5**). However, characteristics including smooth surface and the center ulcer were correlated with malignant risk of GST (**Table 5**). To exactly explore the indexes for predicting prognosis, we created a statistical correlation of EUS indexes (**Table 6**). We found that the smooth surface and center ulcer had significant correlation ($P < 0.0001$).

Discussion

Gastric submucosal tumors (SMT) account for 3% of gastric neoplasm, including mesenchymal tissue tumors and stomach nervous tissue tumors. GST was first identified by Mazur in 1983 as a kind of SMT consisting of undifferentiated or pluripotent spindles and epithelioid cells. The common SMT location had not yet been reported. In our study, we found that SMTs are most commonly found in the stomach fundus (56.3%), gastric body (30.5%), and sinuses ventriculi (13.1%). In large population-based studies, approximately 70% of SMT patients were clinically symptomatic. The most common presenting symptoms were gastric bleeding, abdominal pain, and the presence of a palpable mass [11-14]. In our study, the symptoms were various, such as abdominal pain, hematemesis, and melena.

Table 3. Comparison of the EUS indexes of GSTs and non-GSTs

Index	GST	Non-GST	*P* value
Tumor diameter (cm)	4.31±0.19	2.9±1.78	0.01
Age (years)	59.5±11.4	49.6±13.0	0.000
Tumor diameter (cm)			0.000
< 2	26	19	
2-5	79	37	
> 5	45	7	
Gender			0.5027
Male	67	25	
Female	83	38	
Lesion site			0.8946
Fundus of stomach	84	36	
Gastric body	47	18	
Sinuses ventriculi	19	9	
Smooth surface			0.1836
Yes	78	41	
No	22	6	
Ulcer in the center			0.3752
Present	23	7	
Absent	62	29	
Mucosal bridge			0.053
Present	38	9	
Absent	45	25	
Uniformity echo			0.001
Yes	47	35	
No	62	14	
Clear boundary			0.7191
Yes	93	45	
No	7	2	
Shape			0.7752
Hemispherical	11	4	
Irregular	89	43	
Concurrent bleeding			0.0378
Yes	23	3	
No	127	60	

GST: gastric stromal tumor.

Endoscopy alone had suboptimal accuracy of as low as 40% for identifying the cause of submucosal bulges [15]. Usually the mucosal surface is normal, and conventional forceps biopsy results are frequently negative. Other noninvasive imaging methods such as CT and barium meal are also suboptimal for evaluating submucosal indentations.

EUS combined the endoscopic view with ultrasonographic images generated by a high-frequency intraluminal probe. EUS clearly showed the five-layer stomach structure and accurately detected the tumor origin, focal size, amount, boundary, and echo, a useful method for diagnosing GST. EUS showed that GSTs had low-level echo, clear boundaries, and smooth edges [16, 17]. Nevertheless, the EUS diagnosis basis is presumptive and cannot replace a histological diagnosis of GST. EUS also easily misdiagnoses some SMTs such as GST such as leiomyoma, lipomyoma, and schwannoma. In our study, schwannoma, leiomyoma, heterotopic pancreas, vascular malformation, polypus, cyst, stomach repeat deformity, ectopic spleen, glomus tumors, nodular fibrous pseudotumors, and inflammatory myofibroblastic tumors were diagnosed as GSTs. They had overlapping echo and endoscopic features and could not be accurately determined without a biopsy sample [18, 19]. Schwannoma, leiomyoma, polypus, glomus tumors, nodular fibrous pseudotumors, and inflammatory myofibroblastic tumors were neoplastic SMTs that just required a local excision. Heterotopic pancreas, vascular malformation, cyst, stomach repeat deformity, and ectopic spleen were benign SMTs that could be followed without intervention [20]. So, definite GST diagnosis using EUS before operation is very important.

In our study, we explored some misdiagnosis factors using EUS such as tumor diameter, age, gender, and a series of EUS characteristics. The average tumor diameters of GSTs and non-GSTs were 4.31±3.19 cm and 2.9±1.78 cm, respectively, and the *P* value was 0.01 (**Table 3**), so we deduced that size was perhaps a misdiagnosis factor. To accurately evaluate the effects of tumor diameter on misdiagnosis, we compared the misdiagnosis rates of different tumor diameters in **Table 3**. We found that the *P* value was 0.000. Therefore, we concluded that a tumor with a diameter < 2 cm was much more easily misdiagnosed, and the misdiagnosis rate of tumors with diameters > 5 cm was obviously lower. We should thus diagnose and treat the SMTs with diameters < 2 cm cautiously. The ESMO/European Sarcoma Network Working Group held that the standard approach to patients with small gastric nodules less than 2 cm in size is a EUS assessment and then an annual follow-up, reserving excision for patients whose tumors increase in size or become symptomatic [21]. Age and concurrent bleeding may

Table 4. The relationship between the EUS indexes and tumor size

Index	Num	Tumor diameter (cm)	*P* value
Smooth surface			< 0.0001
Yes	119	5.30±3.72	
No	28	3.05±1.75	
Ulcer in the center			< 0.0001
Present	30	2.90±1.74	
Absent	91	4.41±1.76	
Mucosal bridge			0.3343
Present	47	3.12±2.12	
Absent	70	3.47±1.58	
Uniformity echo			< 0.0001
Yes	82	4.31±2.34	
No	76	2.77±1.66	
Shape			< 0.0001
Hemispherical	15	5.85±3.11	
Irregular	132	3.21±1.83	
Clear boundary			0.211
Yes	139	4.37±1.76	
No	9	3.45±2.15	

also have been misdiagnosis factors, as shown in **Table 3**. GST mainly occurred in elderly patients, and younger patients were easier to misdiagnose. The misdiagnosis rate of GST hemorrhage is obviously lower, so we preferentially considered gastrointestinal mesenchymal neoplasms concurrent bleeding as GSTs. We also evaluated the effects of gender and lesion site on the misdiagnosis, and *p* values were 0.5027 and 0.8946, respectively, with no statistical differences. The gender and lesion site had nothing to do with the misdiagnosis. At last, we estimated the effects of EUS characteristics on misdiagnosis. We found that the mucosal bridge and echo participated in misdiagnosis. The tumors with uniformity echo or without the mucosal bridge were easier to be misdiagnosed as GSTs. Coincidently, just 2 patients in our study were shown with high-level echo and proved to be non-GSTs by pathology. So, we should also pay attention to tumors with high-level echo.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) with a 22-gauge needle or core tissue examination, respectively, has emerged as a minimally invasive technique that allows identification and sampling of various SMTs and extraintestinal mass lesions [22-23]. Kazuya evaluated the role of EUS-FNA in the preoperative diagnosis of 29 GST patients, with the final diagnosis by surgical resection, and found that the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 100%, 80%, 96%, 100%, and 97%, respectively [24]. Stelow studied the uses of immunocytochemical analysis with material procured by EUS-FNA for the diagnosis of 95 patients of subepithelial intramural gastrointestinal mesenchymal neoplasms and found that, when sufficient material was present, immunocytochemical analysis used with material obtained by EUS-FNA was highly predictive of final pathologic diagnosis [25]. Chatzipantelis evaluated the efficacy and accuracy of EUS-FNA in diagnosing GSTs and demonstrated that EUS-FNA provided accurate GST diagnosis in combination with immunohistochemical reactivity for a c-kit, performed with adequate cytology specimens obtained by FNA [26]. A series of recent research showed that EUS-FNA with immunohistochemical analysis was a safe and accurate method in the pretherapeutic diagnosis of GST. It should be taken into consideration in decision-making, especially at early diagnosis following minimally invasive surgery for GST [27-29].

GSTs are now considered potentially malignant and have the risk of metastatic relapse, so they need to be resected, even small intramural lesions of the GI tract [4, 5]. Predicting malignant risk is important for clinicians because the resection of all incidental small-sized GSTs with low malignancy risk may not be needed [21]. Clinical malignancy risk was determined by tumor size and mitotic index [30, 31]. Although the preoperative estimate of risk could be made from tumor size, the mitotic index could not be known before surgical resection.

In 2009, Shaph determined which EUS characteristics correlated with malignant GST potential and found that EUS characteristics like tumor size, extraluminal border, depth, and heterogeneity could be used to predict malignant GST potential. However, the conclusion needed to be confirmed due to the limited number of study cases [32]. Later, Mi Na Kim designed an experiment to determine whether EUS features could preoperatively predict the medium-sized GSTs' malignancy risk, and the results showed that EUS features could not be used to preoperatively predict medium-sized GSTs' malignan-

Table 5. Comparison of the EUS indexes with malignant risk of GST

Index	Risk of Aggressive Behavior				*P* value
	Very low	Low	Moderate	High	
Age (years)	60.56±10.09	59.17±11.97	57.64±12.31	61.2±11.36	0.6355
Tumor diameter (cm)	1.45±0.55	3.28±1.14	5.83±1.89	7.69±5.20	< 0.0001
Ki67 index	(1.27±2.05)%	(3.42±2.91)%	(6.44±16.20)%	(9.46±7.54)%	0.005
Gender					0.082
Male	10	27	14	17	
Female	17	36	22	8	
Lesion site					0.2214
Fundus of stomach	16	39	15	14	
Gastric body	10	14	15	8	
Sinuses ventriculi	1	10	6	2	
Smooth surface					0.0571
Yes	18	38	13	8	
No	1	10	8	4	
Ulcer in the center					0.0184
Present	1	13	2	6	
Absent	17	29	11	5	
Mucosal bridge					0.7059
Present	6	20	8	5	
Absent	11	22	7	4	
Uniformity echo					1.068
Yes	13	22	8	4	
No	8	28	16	10	
Clear boundary					0.9387
Yes	17	45	18	13	
No	1	3	2	1	
Shape					1.1333
Hemispherical	1	3	5	2	
Irregular	18	45	16	10	
Concurrent bleeding					0.0492
Yes	1	11	10	1	
No	26	52	26	23	

cy risk [33]. In our study, the EUS characteristics like the mucosal bridge, uniformity echo, clear boundary, and shape did not differ significantly among very low, low, moderate, and high risk groups. However, the smooth surface, center ulcer, and concurrent bleeding were potential prognostic factors of GST. As shown in **Table 6**, the smooth surface and center ulcer were correlative indexes and could predict malignant risk synergistically.

In the previous study, Sakamoto evaluated whether assessing tumor vascularity using contrast-enhanced harmonic EUS (CEH-EUS) could predict the preoperative malignancy risk of GSTs. The results demonstrated that CEH-EUS successfully visualized intratumoral vessels and may play an important role in predicting GST malignancy risk [34]. Another study observed that GST intratumoral vessels using CEH-EUS were correlated with a higher degree of angiogenesis, resulting in higher malignant potential [35]. However, CEH-EUS could not distinguish other gastric submucosal tumors (leiomyoma, schwannoma) from GSTs. So, a new method should be developed to exactly predict GST malignancy risk preoperatively.

Conclusion

GSTs are considered potentially malignant and require resection. The differentiation of GSTs

Table 6. The relationship among EUS indexes

	Smooth surface	Ulcer in the center	Mucosal bridge	Uniformity echo	Shape	Clear boundary
Smooth surface	1	-0.52085	-0.0292	0.31125	0.18568	0.09152
		< 0.0001	0.7588	0.0002	0.0317	0.2966
	147	116	113	142	134	132
Ulcer in the center	-0.52085	1	0.26757	-0.2446	-0.18904	0.02451
	< 0.0001		0.0051	0.0069	0.0412	0.794
	116	121	108	121	117	116
Mucosal bridge	-0.0292	0.26757	1	-0.08431	-0.06085	-0.00562
	0.7588	0.0051		0.3682	0.5239	0.9533
	113	108	117	116	112	111
Uniformity echo	0.31125	-0.2446	-0.08431	1	0.26581	0.25361
	0.0002	0.0069	0.3682		0.0012	0.0021
	142	121	116	158	145	145
Shape	0.18568	-0.18904	-0.06085	0.26581	1	0.25086
	0.0317	0.0412	0.5239	0.0012		0.0029
	134	117	112	145	147	139
Clear boundary	0.09152	0.02451	-0.00562	0.25361	0.25086	1
	0.2966	0.794	0.9533	0.0021	0.0029	
	132	116	111	145	139	147

from benign SMTs, such as leiomyoma or schwannoma, is essential for effective clinical management. EUS is a useful method for diagnosing GSTs, with a misdiagnosis rate of 29.6%, and definite diagnosis relies on immunohistochemical analysis. Tumor diameter, age, concurrent bleeding, and EUS characteristics such as the mucosal bridge and echo may be the misdiagnosis factors. Concurrent bleeding and EUS indexes of the smooth surface and center ulcer are potential prognostic factors of GST.

Acknowledgements

This study was supported by the Grants for Key Medical Department in Jiangsu Province, Outstanding Medical Researchers in Jiangsu Province, and Natural Science Fund of China (81201621).

Disclosure of conflict of interest

None.

Address correspondence to: De-Cai Yu and Yi-Tao Ding, Department of General Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing 210008, Jiangsu Province, P. R. China. E-mail: dryudecai@qq.com (DCY); drdingyitao@sina.com (YTD)

References

[1] Blay JY, Bonvalot S, Casali P, Choi H, Debiec-Richter M, Dei Tos AP, Emile JF, Gronchi A, Hogendoorn PC, Joensuu H, Le Cesne A, McClure J, Maurel J, Nupponen N, Ray-Coquard I, Reichardt P, Sciot R, Stroobants S, van Glabbeke M, van Oosterom A, Demetri GD; GIST consensus meeting panelists. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. Ann Oncol 2005; 16: 566-578.

[2] Sarlomo-Rikala M, Kovatich AJ, Barusevicius A, Miettinen M. CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod Pathol 1998; 11: 728-734.

[3] Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod Pathol 2000; 13: 1134-1142.

[4] Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002; 33: 459-465.

[5] Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clini-

copathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005; 29: 52-68.
[6] Landi B. [Gastrointestinal stromal tumors: clinical features and diagnosis]. Bull Acad Natl Med 2012; 196: 845-52; discussion 52-53.
[7] Zanghi G, Di Stefano G, Di Dio D, D'Agati V, Benfatto G, Basile F. [Gastrointestinal stromal tumors: diagnosis and treatment. Our experience]. G Chir 2011; 32: 29-33.
[8] Chien CH, Chien RN, Yen CL, Fang KM, Liu CJ, Lin CL, Chang JJ, Chen LW, Lee TS, Chen SW, Hu CC, Chang LC. The role of endoscopic ultrasonography examination for evaluation and surveillance of gastric subepithelial masses. Chang Gung Med J 2010; 33: 73-81.
[9] Szukics B, Wagner A. [Diagnostic endoscopy and endoscopic ultrasonography of gastrointestinal stroma tumors]. Radiologe 2009; 49: 1117-1121.
[10] Ji F, Wang ZW, Wang LJ, Ning JW, Xu GQ. Clinicopathological characteristics of gastrointestinal mesenchymal tumors and diagnostic value of endoscopic ultrasonography. J Gastroenterol Hepatol 2008; 23: e318-324.
[11] Tryggvason G, Kristmundsson T, Orvar K, Jonasson JG, Magnusson MK, Gislason HG. Clinical study on gastrointestinal stromal tumors (GIST) in Iceland, 1990-2003. Dig Dis Sci 2007; 52: 2249-2253.
[12] Al-Thani H, El-Menyar A, Rasul KI, Al-Sulaiti M, El-Mabrok J, Hajaji K, Elgohary H, Tabeb A. Clinical presentation, management and outcomes of gastrointestinal stromal tumors. Int J Surg 2014; 12: 1127-1133.
[13] Asija AP, Mejia AV, Prestipino A, Pillai MV. Gastrointestinal Stromal Tumors: A Review. Am J Ther 2013; 23: e550-7.
[14] Ichiyanagui Rodriguez C, Frisancho O, Yabar A. [Clinical, endoscopic and histologic profile of the Gastrointestinal Stromal Tumours in the Rebagliati Hospital]. Rev Gastroenterol Peru 2010; 30: 201-210.
[15] Rosch T, Kapfer B, Will U, Baronius W, Strobel M, Lorenz R, Ulm K. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. Scand J Gastroenterol 2002; 37: 856-862.
[16] Gheorghe C, Borca A, Gheorghe L. The role of EUS for accurate preoperative differential diagnosis between GIST and pancreatic rest. J Gastrointestin Liver Dis 2012; 21: 442-443.
[17] Szukics B, Wagner A. [Diagnostic endoscopy and endoscopic ultrasonography of gastrointestinal stroma tumors]. Radiologe 2009; 49: 1117-1121.
[18] Moon JS. Endoscopic ultrasound-guided fine needle aspiration in submucosal lesion. Clin Endosc 2012; 45: 117-123.
[19] Rong L, Kida M, Yamauchi H, Okuwaki K, Miyazawa S, Iwai T, Kikuchi H, Watanabe M, Imaizumi H, Koizumi W. Factors affecting the diagnostic accuracy of endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) for upper gastrointestinal submucosal or extraluminal solid mass lesions. Dig Endosc 2012; 24: 358-363.
[20] Kobara H, Mori H, Fujihara S, Nishiyama N, Tsutsui K, Masaki T. Gastric heterotopic pancreas can be identified by endoscopic direct imaging with submucosal endoscopy. J Gastrointestin Liver Dis 2013; 22: 345-348.
[21] Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 23 Suppl 2012; 23 Suppl 7: 49-55.
[22] Vander Noot MR 3rd, Eloubeidi MA, Chen VK, Eltoum I, Jhala D, Jhala N, Syed S, Chhieng DC. Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer 2004; 102: 157-163.
[23] Chen VK, Eloubeidi MA. Endoscopic ultrasound-guided fine-needle aspiration of intramural and extraintestinal mass lesions: diagnostic accuracy, complication assessment, and impact on management. Endoscopy 2005; 37: 984-989.
[24] Akahoshi K, Sumida Y, Matsui N, Oya M, Akinaga R, Kubokawa M, Motomura Y, Honda K, Watanabe M, Nagaie T. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. World J Gastroenterol 2007; 13: 2077-2082.
[25] Stelow EB, Murad FM, Debol SM, Stanley MW, Bardales RH, Lai R, Mallery S. A limited immunocytochemical panel for the distinction of subepithelial gastrointestinal mesenchymal neoplasms sampled by endoscopic ultrasound-guided fine-needle aspiration. Am J Clin Pathol 2008; 129: 219-225.
[26] Chatzipantelis P, Salla C, Karoumpalis I, Apessou D, Sakellariou S, Doumani I, Papaliodi E, Konstantinou P. Endoscopic ultrasound-guided fine needle aspiration biopsy in the diagnosis of gastrointestinal stromal tumors of the stomach. A study of 17 cases. J Gastrointestin Liver Dis 2008; 17: 15-20.
[27] Hoda KM, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. Gastrointest Endosc 2009; 69: 1218-1223.
[28] Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. Nat Rev Gastroenterol Hepatol 2009; 6: 363-371.

[29] Hussain T, Salamat A, Farooq MA, Hassan F, Hafeez M. Indications for endoscopic ultrasound and diagnosis on fine-needle aspiration and cytology. J Coll Physicians Surg Pak 2009; 19: 223-227.
[30] Hornick JL, Fletcher CD. The role of KIT in the management of patients with gastrointestinal stromal tumors. Hum Pathol 2007; 38: 679-687.
[31] Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23: 70-83.
[32] Shah P, Gao F, Edmundowicz SA, Azar RR, Early DS. Predicting malignant potential of gastrointestinal stromal tumors using endoscopic ultrasound. Dig Dis Sci 2009; 54: 1265-1269.
[33] Kim MN, Kang SJ, Kim SG, Im JP, Kim JS, Jung HC, Song IS. Prediction of risk of malignancy of gastrointestinal stromal tumors by endoscopic ultrasonography. Gut Liver 2013; 7: 642-647.
[34] Sakamoto H, Kitano M, Matsui S, Kamata K, Komaki T, Imai H, Dote K, Kudo M. Estimation of malignant potential of GI stromal tumors by contrast-enhanced harmonic EUS (with videos). Gastrointest Endosc 2011; 73: 227-237.
[35] Yamashita Y, Kato J, Ueda K, Nakamura Y, Abe H, Tamura T, Itonaga M, Yoshida T, Maeda H, Moribata K, Niwa T, Maekita T, Iguchi M, Tamai H, Ichinose M. Contrast-enhanced endoscopic ultrasonography can predict a higher malignant potential of gastrointestinal stromal tumors by visualizing large newly formed vessels. J Clin Ultrasound 2015; 43: 89-974.