Esophageal Gastrointestinal Stromal Tumor

Is Tumoral Enucleation a Viable Therapeutic Option?

W. B. Robb, MD,†‡ E. Bruyere, MD, PhD,*†‡§ D. Amielh, MD,* E. Vinatier, MD,* J. Y. Mabrut, MD, PhD,¶ T. Perniceni, MD,‖ G. Piessen, MD, PhD,*†‡§ and Christophe Mariette, MD, PhD*†‡§; on-behalf-of the FREGAT Working Group—FRENCH*

Objective: The primary objective was to evaluate the feasibility of surgical enucleation of esophageal gastrointestinal stromal tumors (E-GISTs). Secondary objectives evaluated (i) the impact of tumor enucleation on oncological outcomes, (ii) the effect of pretherapeutic biopsy on the feasibility of E-GIST enucleation, and (iii) the impact of mucosal ulceration on outcome.

Background: E-GISTs are very rare tumors and esophageal resection has been the recommended approach. The feasibility and impact on outcomes of tumor enucleation are unknown.

Methods: Through a large national multicenter retrospective study, 19 patients with E-GISTs were identified between 2001 and 2010. Patients who underwent either enucleation or esophagectomy were compared.

Results: Of over 19 patients identified with E-GISTs, curative treatment was surgical for 16 patients, with enucleation in 8 and esophagectomy in 8. In the enucleation group, median tumoral diameter was 40 mm (18–65 mm), without any mucosal ulceration, preoperative capsular ruptures, or incomplete resections. In the esophagectomy group, the median tumoral diameter was 85 mm (55–250 mm), with mucosal ulceration in 4 patients, preoperative capsular rupture in 1, and no incomplete resections. Severe postoperative complication rates were 50% and 25% in the esophagectomy and enucleation groups, respectively, with 2 postoperative deaths after esophagectomy. After a median follow-up of 6.4 years, 2 recurrences were observed after esophagectomy versus 0 after enucleation. Endoscopic biopsies did not expose patients to complications or local recurrence after enucleation. Endoscopic mucosal ulceration was associated with more aggressive tumors.

Conclusions: E-GIST enucleation seems safe for tumors of less than 65 mm in diameter.

Keywords: enucleation, esophagus, gastrointestinal stromal tumor, GIST, surgery

(*Ann Surg* 2014;00:1–8)

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract and for the most part occur in the stomach (60%–70%) and small intestine (20%–30%).[1–3] Esophageal gastrointestinal stromal tumors (E-GISTs) are extremely uncommon, accounting for 0.7% of all GISTs.[4] As with most rare pathologies, many questions remain unanswered regarding their optimal management. Although pathological series of E-GISTs has been published,[1,5] the reporting of surgical series has been limited to individual case reports and case series of small numbers.[6–13] Not only are E-GISTs less common than abdominal GISTs, but the esophagus also differs anatomically, lacking both a confining serosal layer and a mesentery, meaning that segmental or wedge resections used for stomach and small intestinal GISTs are not feasible. Esophagectomy is an operation with a significant morbidity[14] whose systematic use for small E-GISTs, with low malignant potential, seems questionable. The other surgical option is tumor enucleation, an approach that preserves the esophagus. Concerns exist that tumor enucleation could lend itself to incomplete tumor resection, with a higher risk of disrupting the tumor capsule and hence compromised oncological outcomes. The optimal surgical approach, therefore, remains to be defined and tailored to malignant risk.

Previously E-GISTs were confused with leiomyomas, leiomyoblastomas, and leiomyosarcomas; however, immunohistochemical staining for CD117 and CD34 has distinguished them from these other esophageal tumors.[2,3,5] Preoperative biopsy or fine-needle aspiration cytology (FNAC) provides one possible means of differentiating E-GISTs from benign lesions and may guide decisions regarding the necessity and radicality of resection. Whether preoperative biopsies have an impact on the feasibility of surgical enucleation or oncological outcomes has not been established.

The aim of this study was consequently to evaluate (i) the feasibility and oncological outcomes of E-GIST enucleation, (ii) the impact of diagnostic tumor sampling on the feasibility of enucleation, and (iii) the impact of mucosal ulceration on outcome.

METHODS

A database was established for all patients diagnosed with an E-GIST between 2001 and 2010 in all 29 metropolitan University Hospital Centres in France, through the FREGAT (French EsoGastric Tumors working group) network. All patients with a histopathologically confirmed E-GIST were retrospectively included and were identified by an exhaustive search of pathological databases using diagnostic codes, no matter what the treatment plan. In France, before a histopathological diagnosis of a GIST being made, all specimens and pathological slides must be read by 2 specialist gastrointestinal pathologists, providing an internal quality control for the diagnosis. Moreover, for the present study, pathological reports were systematically collected for all patients and the robustness of the pathological diagnosis was reviewed, allowing for an external control for the quality of diagnosis. The decision as to which operative procedure was performed was made by each individual surgeon in conjunction with the local multidisciplinary team.

Data on patient demographics, clinical presentation, use of diagnostic biopsy, operative technique, histopathology, postoperative course, and oncological outcomes were gathered and analyzed. Disease recurrence was classified as either being local (limited to the site

From the *Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Lille, France; †North of France University, Lille, France; ‡Integrated Research Center in Oncology: SIRIC ONCOLille, Lille, France; §Inserm, UMR837, Jean-Pierre Aubert Research Center, Team 5 Mucins, Epithelial Differentiation and Carcinogenesis, Lille, France; ¶University Hospital Croix-Rousse, Lyon, France; and ‖Institut Mutualiste Montsouris, Paris, France.

FREGAT: French Esogastric Tumor working group

FRENCH: French Federation of Surgical Research (Fédération Française de Chirurgie)

Disclosure: The authors declare no conflicts of interest.

Reprints: Christophe Mariette, MD, PhD, Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Regional University Hospital Center, Place de Verdun, 59037, Lille Cedex, France. E-mail: christophe.mariette@chru-lille.fr.

Copyright © 2014 by Lippincott Williams & Wilkins

ISSN: 0003-4932/14/00000-0001

DOI: 10.1097/SLA.0000000000000505

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

of surgical resection), regional (within the regional resection area), or distant recurrence. Mixed recurrences included concomitant locoregional and distant relapses. Mitotic index was defined by the number of mitoses per 50 high-powered fields (hpf) ($\leq$5 per 50 hpf, $>$5 to $\leq$10 per 50 hpf, and $>$10 per 50 hpf). Decisions regarding the administration of neoadjuvant and adjuvant tyrosine kinase inhibitors (TKIs) were made at the discretion of the local multidisciplinary teams according to the national guidelines.[15] The study complied with the French National Health guidelines for research involving human subjects.

All collected data were entered into a dedicated database and were analyzed using SPSS version 19.0 software (SPSS, Chicago, IL). Data are shown as prevalence or median (range). As the sample size is small, dedicated statistical tests were used. Ordinal data comparing patient, tumor, surgical, and oncological outcomes after esophagectomy or enucleation were compared using the Fisher exact test, whereas continuous data were compared using the nonparametric Whitney-Mann *U* test. All tests were 2 sided, and *P* values less than 0.05 were considered to be statistically significant. The survival status of patients was determined in January 2013 and no patients were lost to follow-up. The median follow-up was 77 months (range, 23–135 months), similar between the esophagectomy—76 months (range, 23–135 months)—and enucleation—77 months (range, 26–123 months)—groups ($P = 1.000$).

RESULTS

Characteristics of Overall and Resected Populations

A total of 19 patients were identified who had a histologically proven diagnosis of an E-GIST. There were 5 men (26.3%) and 14 women (73.7%), with a median age of 61 years (24–88 years). The most common presenting symptom was dysphagia (n = 6), whereas 7 patients were diagnosed incidentally—3 during endoscopy and 4 after unrelated radiological investigation.

Three patients did not undergo surgical resection because of the presence of hepatic metastases at the time of diagnosis (n = 2) or advanced age (n = 1; 88 years old). For those 3 patients, the tumor was located in the proximal (n = 1) or middle third (n = 2) of the esophagus, with 2 of these 3 patients having evidence of mucosal ulceration on diagnostic endoscopy. They were all treated by TKI and 1 benefited from an endoscopic stenting.

TABLE 1. Patient, Surgical, and Tumor Characteristics in Patients Undergoing Resection (n = 16)

Variables	Resected Patients (n = 16)	Esophagectomy (n = 8)	Enucleation (n = 8)	*P*
ASA score				
1	11	5	6	0.580
2	4	2	2	
3	1	1	0	
Neoadjuvant treatment				
No	14	6	8	0.467
Yes	2	2	0	
Mucosal ulceration				
No	12	4	8	0.077
Yes	4	4	0	
Thoracotomy				
No	6	0	6	0.007
Yes	10	8	2	
Laparotomy				
No	7	0	7	0.001
Yes	9	8	1	
Duration of operation,* min	152.5 (60–420)	400 (300–420)	110 (60–180)	0.025
Length of stay*, d	9 (2–32)	11.5 (8–32)	5.5 (2–15)	0.013
Tumor size,* mm	60 (18–250)	85 (55–250)	40 (18–65)	0.001
Mitotic index				
<5/50 hpf	8	4	4	1.000
6–10/50 hpf	2	1	1	
>10/50 hpf	6	3	3	
Breach of tumor capsule				
No	15	7	8	0.302
Yes	1	1	0	
Circumferential margin, mm				
0	11	5	6	0.809
1	2	1	1	
2	3	2	1	
Postoperative morbidity (<30 d)				
No	10	4	6	0.302
Yes	6	4	2	
Death during hospitalization				
No	14	6	8	0.467
Yes	2	2	0	

*Median values (range).

© 2014 Lippincott Williams & Wilkins

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

TABLE 2. Malignant Risk, Mucosal Ulceration, Preoperative Biopsy, and Disease Recurrence

Patient/ Resection	Age/Sex	Size, mm	Mitotic Index (Mitoses/hpf)	Malignant Risk[16]	Mucosal Ulceration	Biopsy	Preoperative Breach of Capsule	Neoadjuvant And/or Adjuvant Therapy	Disease Recurrence/ Metastases
1/enucleation	68/female	18	6–10/50 hpf	Intermediate	No	Yes	No	Adjuvant	No
2/enucleation	47/female	18	≤5/50 hpf	Very low	No	Yes	No	No	No
3/enucleation	45/male	20	>10/50 hpf	High	No	No	No	No	No
4/enucleation	49/male	40	≤5/50 hpf	Very low	No	No	No	No	No
5/enucleation	61/female	40	>10/50 hpf	High	No	No	No	Adjuvant	No
6/enucleation	44/female	42	≤5/50 hpf	Very low	No	No	No	No	No
7/enucleation	68/female	45	≤5/50 hpf	Low	No	No	No	No	No
8/enucleation	53/male	65	>10/50 hpf	High	No	Yes	No	No	No
1/esophagectomy	64/female	55	>10/50 hpf	High	Yes	Yes	No	No	NA
2/esophagectomy	55/male	75	≤5/50 hpf	Intermediate	No	Yes	No	Neoadjuvant and Adjuvant	No
3/esophagectomy	71/female	80	>10/50 hpf	High	Yes	Yes	Yes	Adjuvant	No
4/esophagectomy	54/female	80	≤5/50 hpf	Intermediate	Yes	Yes	No	No	No
5/esophagectomy	24/female	90	6–10/50 hpf	High	No	No	No	No	No
6/esophagectomy	77/female	95	≤5/50 hpf	Intermediate	No	Yes	No	Neoadjuvant	NA
7/esophagectomy	56/male	100	>10/50 hpf	High	Yes	Yes	No	No	Yes
8/esophagectomy	76/female	250	≤5/50 hpf	High	No	No	No	No	Yes

NA indicates not applicable because of postoperative death.

TABLE 3. Immunohistochemical Findings of E-GISTs

Antigen	Specimen Positiven (%)
CD34	14/16 (87.5)
CD117	14/16 (87.5)
S100	4/16 (25.0)
Bcl2	0/16 (0)
Actine1	3/16 (18.8%)
Desmine1	7/16 (43.8%)

Sixteen patients underwent surgical resection—8 had an esophagectomy and 8 had a tumor enucleation. Eleven of the 16 patients undergoing surgery were female and 15 were American Society of Anaesthesiologists (ASA) score I or II (Table 1). Six tumors were located in the proximal third, 9 in the middle third, and 1 in the distal third of the esophagus. All resected patients underwent a diagnostic endoscopy and staging computerized tomography scan; 5 patients underwent an endoscopic ultrasound and 2 a positron emission tomography scan. No resected patients had evidence of distant metastasis on staging computerized tomography scan. Of the 16 resected patients, 4 had evidence of mucosal ulceration on endoscopic examination. Two patients diagnosed with a locally advanced tumor (median diameter 85 mm vs 50 mm for nonlocally advanced tumors) underwent neoadjuvant treatment with TKI.

Surgical Approach

In view of the historical absence of recommendations regarding the surgical management of E-GISTs, the decision whether an enucleation or esophagectomy was performed was made by each individual surgeon in conjunction with the local multidisciplinary team. Eight patients underwent esophagectomy and 8 underwent tumor enucleation, with excision of the surrounding muscularis and without mucosal resection. Seven patients undergoing esophagectomy had a 2-stage operation by open laparotomy and thoracotomy with an intrathoracic anastomosis, and 1 patient had a 3-stage esophagectomy with cervical anastomosis. Of the 8 patients undergoing surgical enucleation, 5 were completed thoracoscopically (median tumor size, 42 mm; range, 18–45 mm), 1 thoracoscopic resection was converted to open thoracotomy due to a 40-mm tumor involving a large circumference of the esophageal wall, 1 enucleation was performed by a laparoscopic transhiatal approach for a 18-mm tumor, and 1 enucleation was performed by planned open thoracotomy for a 20-mm tumor. No patient was converted intraoperatively from a planned enucleation to an esophagectomy. The median duration of hospital stay was significantly longer in patients undergoing esophageal resection (11.5 days; range, 8–32 days) than in those undergoing enucleation (5.5 days; range, 2–15 days; $P = 0.013$) as was the median duration of operation—400 minutes (range, 300–420 minutes) versus 110 minutes (range, 60–180 minutes) ($P = 0.025$) (Table 1).

A total of 6 patients had a complicated postoperative recovery (Table 1): 2 patients having a pulmonary embolus, 2 patients a documented pneumonia, 1 patient a chylothorax, and 1 patient an anastomotic leak. There were 2 postoperative deaths, both occurring in patients undergoing esophagectomy, one after massive pulmonary embolism and one because of acute respiratory distress syndrome after extensive pneumonia. All 4 patients undergoing an adjuvant therapy were treated with a TKI—the 2 patients receiving a TKI after esophagectomy did so for 12 months and the 2 patients being so treated after enucleation continued a TKI for a period of 4 and 12 months. There was no statistical difference regarding tumor location, ASA score, administration of neoadjuvant treatment, or the mitotic index of tumors dependent on surgical technique ($P > 0.05$) (Table 1). No patients undergoing an enucleation and 4 having an esophagectomy had evidence of mucosal ulceration on endoscopy ($P = 0.077$). As expected, extended resections to adjacent organs were performed only in patients having an esophagectomy, with 1 patient undergoing an en bloc resection of the tail of the pancreas, spleen, and diaphragm.

Tumor Size, Resection Margins, and Histopathology

The largest tumor undergoing enucleation measured 65 mm, whereas the largest tumor being excised by esophagectomy was 250 mm. The median size of enucleated tumors was 40 mm (range, 18–65 mm), whereas the median size of tumors for which esophagectomy was performed was 85 mm (range, 55–250 mm), ($P = 0.001$)

© 2014 Lippincott Williams & Wilkins

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

TABLE 4. Follow-up and Oncological Outcomes in Patients Discharged From Hospital (n = 14)

Variables	Resected Patients (n = 14)	Esophagectomy (n = 6)	Enucleation (n = 8)	*P*
Adjuvant treatment				
No	10	4	6	0.594
Yes	4	2	2	
Recurrence or metastasis				
No	12	4	8	0.165
Yes	2	2	0	
Local recurrence				
No	13	5	8	0.429
Yes	1	1	0	
Regional recurrence				
No	13	5	8	0.429
Yes	1	1	0	
Metastases				
No	12	4	8	0.165
Yes	2	2	0	
Death				
No	11	5	8	0.419
Yes	3	1	0	

(Table 1), reflecting that tumor size is a significant factor when considering the safety and feasibility of enucleation. All specimens underwent standard pathological preparation and immunohistochemical analysis to make the diagnosis of a GIST. Only one patient, who underwent an esophagectomy for an 80-mm E-GIST, was noted to have breach of the tumor capsule (Patient 3Eso phagectomy, Table 2) intraoperatively, and this was confirmed both on macroscopic and microscopic examination of the tumor specimen. No other patient had either macroscopic or microscopic evidence of capsular disruption, and no difference was noted in the circumferential resection margins depending on the operative technique ($P = 0.809$). Tissues from all tumors were analyzed by immunohistochemistry, and their staining patterns are summarized in Table 3. Tumors were defined as staining positively if greater than 10% of tumor cells stained positively. All tumors in this series, which stained positively for CD117, showed CD117 positivity in more than 50% of tumor cells. Similarly for the 14 CD34 positive tumors, all stained strongly (>50% of tumor cells) for CD34.

Oncological Outcomes

After a median follow-up of 6.4 years, of 14 of the 16 resected patients alive after hospital discharge, 2 patients in the esophagectomy group exhibited disease recurrence (Table 4). One death occurred secondary to disease progression, also in the esophagectomy group. Importantly, neither recurrences nor deaths were observed during follow-up after tumor enucleation.

Impact of Preoperative Biopsy

A preoperative biopsy was performed in 9 patients—6 undergoing esophagectomy and 3 undergoing surgical enucleation (Table 5). All patients with evidence of mucosal ulceration (Patients 1, 3, 4, and 7 undergoing esophagectomy—Table 2) underwent biopsy with tissue forceps. Fine-needle aspiration cytology was performed at the time of endoscopic ultrasound for 5 lesions without mucosal ulceration (3 patients undergoing enucleation and 2 undergoing esophagectomy—Table 2). All 5 FNAs used a 22-gauge needle being passed through the channel of the endoscope, and under real-time endoscopic ultrasound guidance the target lesion was punctured with negative pressure applied by the syringe. In all 5 cases, the sufficiency of samples was immediately assessed by a cytopathologist. Biopsy confirmed the diagnosis of an E-GIST in 7 patients (77.8%), with one preoperative biopsy being suggestive of a squamous cell carcinoma and one biopsy result was nondiagnostic. The only patient in whom a thoracoscopic enucleation was converted to an open thoracotomy had not undergone a preoperative biopsy. Oncological resection was not compromised by the performance of preoperative biopsy, with no increased risk of breach of the tumor capsule ($P = 1.000$) or circumferential resection margin positivity ($P = 0.331$), nor was performing a diagnostic biopsy related to increased postoperative morbidity ($P = 0.145$) (Table 5). Overall disease recurrence, and local, regional, and metastatic recurrence showed no correlation with the performance of a diagnostic biopsy ($P > 0.05$).

Impact of Mucosal Ulceration

Four patients, all of whom underwent esophagectomy, had mucosal ulceration evident on preoperative endoscopy in tumors measuring 55, 80, 80, and 100 mm. Mucosal ulceration was more frequent in larger tumors. In the 8 patients undergoing esophagectomy, there was a trend for mucosal ulceration to be related with a higher mitotic index ($P = 0.082$), but it did not correlate with circumferential resection margin positivity. The sole patient to present with regional recurrence after esophagectomy (patient 7Eso phagectomy, Table 2) had a large tumor (100 mm), with the high mitotic index (>10 mitoses/50 hpf) and mucosal ulceration.

DISCUSSION

International clinical guidelines for the management of GISTs have been published by both the European Society of Medical Oncology[17] and the National Comprehensive Cancer Network.[18] They are largely based on evidence coming from more commonly occurring gastric and small intestinal GISTs where malignant potential is known to vary with their size, mitotic index, and anatomical location.[19] To date, little specific data have emerged regarding the appropriate management of the less common E-GISTs. They provide unique surgical challenges as esophageal segmental and wedge resections are not feasible, and hence, the choice of resection lies between esophagectomy, associated with significant morbidity,[14] and surgical tumor enucleation. Enucleation is a less invasive operation,

© 2014 Lippincott Williams & Wilkins

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

TABLE 5. Impact of Preoperative Biopsy

	All Resected Patients (n = 16)			Enucleated Patients (n = 8)		
Variables	**No Biopsy (n = 7)**	**Biopsy (n = 9)**	***P***	**No Biopsy (n = 5)**	**Biopsy (n = 3)**	***P***
Lesion size, mm						
18	0	2		0	2	
20	1	0	—	1	0	—
40	2	0		2	0	
42	1	0		1	0	
45	1	0		1	0	
55	0	1		—	—	
65	0	1		0	1	
75	0	1		—	—	
80	0	2		—	—	
90	1	0		—	—	
95	0	1		—	—	
100	0	1		—	—	
250	1	0		—	—	
Conversion to open operation						
No	6	9	0.438	4	3	1.000
Yes	1	0		1	0	
Postoperative morbidity ≤30 d						
No	1	5	0.145	4	2	1.000
Yes	6	4		1	1	
Breach of mucous membrane at resection						
No	5	3	0.315	5	2	0.375
Yes	2	6		0	1	
Breach of tumor capsule at resection						
No	7	8	1.000	5	3	—
Yes	0	1		0	0	
Circumferential resection margin, mm						
0	5	6	0.331	4	2	0.315
1	0	2		0	1	
2	2	1		1	0	
Local recurrence						
No	6	7*	0.500	5	3	—
Yes	1	0		0	0	
Regional recurrence						
No	7	6*	0.500	5	3	—
Yes	0	1		0	0	
Metastases						
No	6	6*	1.000	5	3	—
Yes	1	1		0	0	

*A total of 7 patients after excluding postoperative death.

but, to be a justified surgical approach to these tumors, it must not lead to incomplete tumor resection, a higher risk of disrupting the tumor capsule or higher rates of disease recurrence.

To provide some answers to these questions, we retrospectively compared outcomes of 16 patients operated on for E-GISTs—8 by esophagectomy and 8 by tumor enucleation. Those undergoing esophagectomy had larger tumors; 2 patients suffered disease recurrence and 1 patient died of progressive disease during follow-up. The largest enucleated tumor was 65 mm in diameter. No patient undergoing enucleation represented with recurrent disease or died of disease progression during follow-up. Enucleation was not found to be more difficult after diagnostic biopsy, and neither enucleation nor biopsy compromised oncological outcomes. This situation parallels that pertaining to duodenal GISTs, where enucleation or limited resection may be performed for small GISTs with low malignant potential, obviating the need for more extensive and morbid surgery.[20] This reflects the established reality that surgical strategy for GISTs differs according to tumor location.[18] Radicality of surgery must therefore be balanced with malignant risk, particularly when considering surgical resection for a tumor that does not disseminate to regional lymph nodes.

Whether esophageal masses should be biopsied to distinguish E-GISTs from morphologically similar but benign lesions has been a matter of controversy. Advances in immunohistochemistry have allowed GISTs to be reliably distinguished by the expression of KIT-protein (CD117), platelet-derived growth factor A and CD34.[21] The staining patterns of the 16 resected E-GISTs (Table 3) confirm a similar spectrum of protein expression as elsewhere in the gastrointestinal tract. Our series shows that diagnostic sampling, by biopsy forceps or FNAC, made the correct preoperative diagnosis in 7 of the 9 cases, a sensitivity of 77.8%. It has commonly been held that performance of a biopsy not only may cause scarring and mucosal adherence that could complicate enucleation, but also may seed tumor cells and potentiate metastatic spread. Current recommendations do not stipulate the need for a preoperative sampling for GISTs elsewhere in the gastrointestinal tract where the diagnosis may be made on typical radiological appearance.[18,21] We did not find evidence in support of either a more difficult dissection or an increased risk of malignant

© 2014 Lippincott Williams & Wilkins

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

TABLE 6. Overview of Available Data: Small Series and Case Reports Regarding E-GIST Enucleation

	Authors								
Variable	**Robb et al (Current Study)**	**von Rahden et al[12]**	**Blum et al[6]**	**Lee et al[11]**	**Jiang et al[9]**	**Koide et al[10]**	**Chang et al[7]**	**Huang et al[8]**	**Yamada et al[13]**
Number E-GISTs in series	19	4	4	7	8	1	1	1–(also 1 liver metastasis—neoadj TKI)	1
Number E-GISTs enucleated	8	4	2	5	3	1	1	1	1
Age (range), yr	44–68	44–57	74–75	39–68	49–64	61	36	38	67
Sex	3 M, 5 F	NS	2 F	5 M	2 M, 1 F	M	1 M	1 M	1 F
Tumor site (range)	3 proximal, 4 middle, 1 lower third	3 middle one third 1 at EGJ	26–36 cm	All in distal one third	24–33 cm	Middle one third	Lower one third	Lower one third	Lower one third
FNA performed	3 pts	NS	Yes	None	None	Yes	Yes	No	No
Ulceration	None	NS	Pt 1—yes Pt 4—no	None	No	No	No	No	No
Operation	5 TE, 2 ThE, 1 LE	1 TE, 2 ThE, and 1 LE	Pt 1—ThE without mucosal resection Pt 4—TE	2 ThE 3 TE	ThE	TE	ThE	LapE	TE
Capsular rupture	None	NS	None (but ulcerated lesion—no mucosal resection)	No	No	No	No	No	No
Lesion size, cm	1.8–6.5	4.0–6.0	Pt 1—12.5 Pt 4—7.2	NS	3.0–7.5	4.5	6.5	3.2	3
Cellular pattern	Spindle	NS	Spindle	NS	Spindle	Spindle	Spindle	Spindle	NS
Mitoses/50 hpf	4 pts ≤5, 1 pts 6–10, 3 pts >10	NS	Pt 1—30 Pt 4—5	NS	<5	<5	NS	>5	<5
Malignant risk	3 very low, 1 low, 1 intermediate, 3 high	NS	Pt 1 very high, Pt 4 intermediate	—	Very low/ intermediate	Very low	NS	NA	Very low
Follow-up	26–123 mos	3 mos	Pt 1—49 mos Pt 4—17 mos	2.2–5.0 yrs	14–202 mos	NS	1 yr	36 mos	NS
Recurrence	None	None	Pt 1—yes Pt 4—no	None (data not known for 1 patient)	None	NS	None	None (after E-GIST enucleation and segmental hepatectomy)	NS

EGJ indicates esophagogastric junction; F, female; LapE, laparotomy and enucleation; LE, laparoscopic enucleation; M, male; NA, not applicable; neoadj TKI, neoadjuvant tyrosine kinase inhibitor; NS, not stated; Pt, patient; TE, thoracoscopic enucleation; ThE, thoracotomy enucleation.

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

© 2014 Lippincott Williams & Wilkins

spread in the 9 patients who underwent a preoperative sampling. Indeed, the only patient who presented with recurrent disease after a diagnostic biopsy had a tumor with high malignant risk (100 mm with >10 mitoses/50 hpf) and had undergone an esophagectomy. None of the 3 patients who had diagnostic FNAC followed by enucleation had disease recurrence nor did enucleation result in intraoperative breach of the mucosa in any of these patients, indicating enucleation after FNAC to be safe.

Current recommendations do not recommend that esophagogastric or small intestinal GISTs of less than 2 cm need be systematically resected as they will be of low risk and their significance remains unclear.[17,18] The standard approach is surveillance with excision reserved for lesions that increase in size or become symptomatic.[17] However, for E-GISTs, as the malignant risk at this site is higher, the implications for surgery are more critical. We demonstrate that diagnosis may be made reliably for E-GISTs on the basis of aspiration cytology and that small lesions may be enucleated safely without high rates of morbidity. We therefore suggest that surgical enucleation of E-GISTs less than 2 cm should be routinely discussed with patients, taking into consideration their age and comorbidities. This strategy also avoids leaving lesions to become larger, resulting with subsequent resections becoming technically more difficult.

Clinical practice guidelines stress the primacy of avoiding intraoperative tumor rupture.[17,18] Despite the lack of a confining serosal surface in the esophagus, we find that enucleation without rupture of the tumor capsule is readily achievable. Other authors have suggested a different experience (Table 6). Blum et al[6] reported a series of 4 E-GISTs and, contrary to our findings, found tumor enucleation to be difficult because of poor tumor coherence and a lack of a true capsule, leading them to recommend esophagectomy for all but the smallest lesions (<2 cm). However, 1 of the 2 E-GISTs in their series undergoing enucleation was large (125 mm) with associated mucosal ulceration on endoscopy, both factors that we suggest may necessitate esophagectomy. In a surgical series of 7 patients with a median follow-up of 4.4 years, Lee et al[11] report no disease recurrence in 5 patients undergoing enucleation, with tumors less than 100 mm, minimal mitotic index, and an intact mucosa, suggesting it to be appropriate and safe in these conditions. In contrast, in 2 patients undergoing esophagectomy, with tumors of more than 100 mm in diameter, evidence of mucosal ulceration, and with a high mitotic activity, tumor recurrence was observed in both patients. A third surgical series[9] has reported the management of 8 E-GISTs and found that 3 of the 4 patients—all of whom had tumors larger than 90 mm and a mitotic index more than 5 mitoses per 50 hpf—died of their disease after surviving postoperatively for 5 years. The authors conclude that tumors more than 90 mm should be regarded as being malignant, necessitating esophagectomy, with esophagectomy also being preferred to enucleation for smaller E-GISTs exhibiting malignant behavior such as mucosal ulceration. Several case reports[7,8,10,13] of successful E-GIST enucleation have been reported in patients being disease free on follow-up. The maximal tumor diameter of in these cases was 65 mm, and none had evidence of mucosal ulceration.

Mucosal ulceration evidently renders enucleation unfeasible and is a finding that strongly suggests the need for esophagectomy. None of the tumors undergoing enucleation in our series had evidence of mucosal ulceration on preoperative endoscopic examination, leading us to suggest that tumors of up to 65 mm in diameter, in the absence of mucosal ulceration, may be safely enucleated without compromising oncological outcomes. The choice between esophagectomy and enucleation for tumors of between 65 and 90 mm needs further clarification, with the decision being influenced by the mitotic index and the presence of mucosal involvement. Tumors of this intermediate size, which are enucleated without capsular disruption but with an intermediate or high mitotic index, should be considered for adjuvant tyrosine kinase treatment, as is the case in other GIST tumor locations. Contrary to other reports,[9] we did not find that esophageal tumor site was of importance in determining prognosis; however, our series includes only one tumor of the distal esophagus with a predominance of middle-third E-GISTs. Whilst recognizing the obvious limitations imposed by the rarity of this pathology on the available evidence, we suggest, on the basis of the totality of the observations published to date (Table 6) and the outcomes we have observed for 8 patients undergoing simple enucleation, a practical algorithm for the surgical management of nonmetastatic E-GISTs (Fig. 1).

We acknowledge that the small population means that statistical analysis and comparisons within our study must be interpreted with some caution. However, we report the largest surgical series of E-GISTs to date, and data on this disease entity will continue to

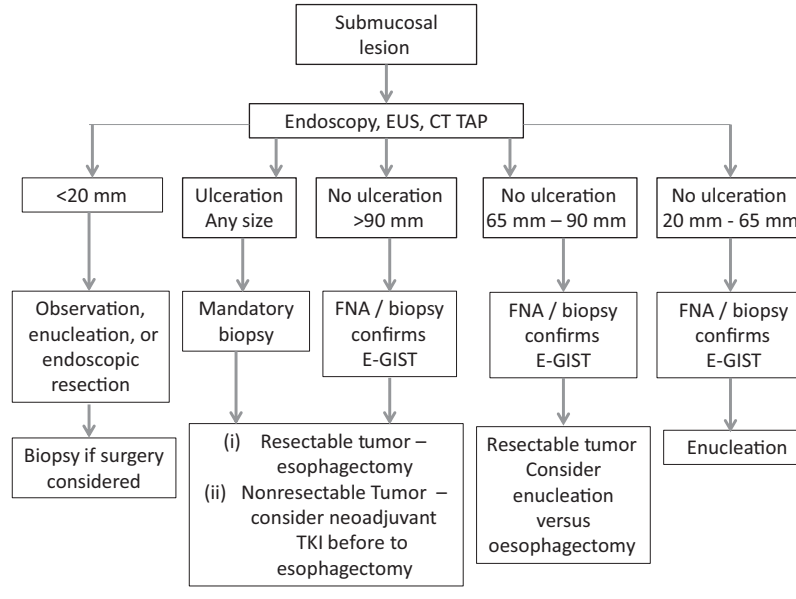

FIGURE 1. Proposed algorithm for surgical management of nonmetastatic E-GISTs (with the limitation of the small sample sizes of the published series). EUS indicates endoscopic ultrasound.

© 2014 Lippincott Williams & Wilkins

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

be limited by its rarity. Even if the median follow-up is 6.4 years, longer-term follow-up will remain important to confirm oncological outcomes remain unchanged.

CONCLUSIONS

E-GISTs are extremely rare tumors. Where there is diagnostic doubt, tumoral sampling may be performed without complicating resection or compromising outcomes. Enucleation is safe for E-GISTs less than 65 mm and should preserve an intact pseudocapsule with negative microscopic margins. Tumors larger than 90 mm with the high mitotic index or other invasive features should undergo resection by esophagectomy.

ACKNOWLEDGMENTS

We thank Professor Emmanuelle Leteurtre for his advice regarding the description of pathological technique and appraisal of results and both Professor Antoine Adenis and Dr Bruno Landi for their critical appraisal and advice regarding our article. We also thank following collaborators: Professor Bernard Meunier, Pontchaillou University Hospital, Rennes; Professor Antoine Hamy, University Hospital, Angers; Professor Pablo Ortega Deballon, University Hospital, Dijon; Professor Christophe Tresallet, Pitié-Salpétrière University Hospital, Paris; Dr Diane Goere, Gustave Roussy Institute, Villejuif; Professor Simon Msika, Louis Mourier University Hospital, Colombes; Professor Denis Pezet, Estaing University Hospital, Clermont-Ferrand; and Dr Henri Mosnier, Croix Saint Simon Hospital, Paris, France.

REFERENCES

1. Abraham SC, Krasinskas AM, Hofstetter WL, et al. "Seedling" mesenchymal tumors (gastrointestinal stromal tumors and leiomyomas) are common incidental tumors of the esophagogastric junction. *Am J Surg Pathol.* 2007;31:1629–1635.
2. Ji F, Wang ZW, Wang LJ, et al. Clinicopathological characteristics of gastrointestinal mesenchymal tumors and diagnostic value of endoscopic ultrasonography. *J Gastroenterol Hepatol.* 2008;23:e318–e324.
3. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med.* 2006;130:1466–1478.
4. Monges G, Bisot-Locard S, Blay JY, et al. The estimated incidence of gastrointestinal stromal tumors in France. Results of PROGIST study conducted among pathologists. *Bull Cancer.* 2010;97:E16–E22.
5. Miettinen M, Sarlomo-Rikala M, Sobin LH, et al. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. *Am J Surg Pathol.* 2000;24:211–222.
6. Blum MG, Bilimoria KY, Wayne JD, et al. Surgical considerations for the management and resection of esophageal gastrointestinal stromal tumors. *Ann Thorac Surg.* 2007;84:1717–1723.
7. Chang WC, Tzao C, Shen DH, et al. Gastrointestinal stromal tumor (GIST) of the esophagus detected by positron emission tomography/computed tomography. *Dig Dis Sci.* 2005;50:1315–1318.
8. Huang CS, Hsu WH, Wu YC, et al. Enucleation of an advanced esophageal gastrointestinal stromal tumor with liver metastasis. *J Gastroenterol Hepatol.* 2006;21:482–483.
9. Jiang P, Jiao Z, Han B, et al. Clinical characteristics and surgical treatment of oesophageal gastrointestinal stromal tumours. *Eur J Cardiothorac Surg.* 2010;38:223–227.
10. Koide N, Kishimoto K, Komatsu O, et al. Thoracoscopic enucleation of esophageal stromal tumor. *Dis Esophagus.* 2004;17:104–108.
11. Lee HJ, Park SI, Kim DK, et al. Surgical resection of esophageal gastrointestinal stromal tumors. *Ann Thorac Surg.* 2009;87:1569–1571.
12. von Rahden BH, Stein HJ, Feussner H, et al. Enucleation of submucosal tumors of the esophagus: minimally invasive versus open approach. *Surg Endosc.* 2004;18:924–930.
13. Yamada H, Shinohara T, Yokoyama K, et al. Thoracoscopic enucleation of esophageal gastrointestinal stromal tumor using prone positioning in a patient with severe chronic obstructive lung disease. *J Laparoendosc Adv Surg Tech A.* 2011;21:635–639.
14. Mariette C, Piessen G, Briez N, et al. Oesophagogastric junction adenocarcinoma: which therapeutic approach? *Lancet Oncol.* 2011;12:296–305.
15. French National Guidelines. Tumeurs stromales gastro-intestinales (GIST). http://www.snfge.org/data/ModuleDocument/publication/5/pdf/TNCD-chapitre-12.pdf. Accessed August 10, 2013.
16. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol.* 2002;33:459–465.
17. ESMO/European Sarcoma Network Working group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2012;23:vii49–55.
18. Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)—update of the NCCN clinical practice guidelines. *J Natl Compr Canc Netw.* 2007;5:S1–29.
19. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol.* 2006;23:70–83.
20. Chung JC, Chu CW, Cho GS, et al. Management and outcome of gastrointestinal stromal tumors of the duodenum. *J Gastrointest Surg.* 2010;14:880–883.
21. Casali PG, Blay JY. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2010;21:v98–102.

© 2014 Lippincott Williams & Wilkins

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.