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A large national comparative study of clinicopathological features and long-term survivals between esophageal gastrointestinal stromal tumor and leiomyosarcoma

Basem Azab [a, *], Francisco Igor Macedo [b], Samuel H. Cass [b], Caroline Ripat [b], Syed S Razi [b], Omar Picado [b], Dido Franceschi [b], Alan S. Livingstone [b], Danny Yakoub [b]

[a] Surgical Oncology, Sentara Careplex Hospital, Sentara Healthcare System, Hampton, VA, USA
[b] Surgical Oncology Division, Department of Surgery, University of Miami, Miami, FL, USA

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ABSTRACT

Background: Esophageal gastrointestinal stromal tumors (E-GIST) and leiomyosarcoma (E-LMS) are rare tumors. Previous studies are limited to small number of patients. We sought to study these two tumors using a large national database.
Methods: The National Cancer Data Base 2004–2014 was queried for patients with E-GIST and E-LMS. The primary outcome was overall survival (OS). Univariate and multivariable Cox regression models were used to investigate OS predictors.
Results: We found 141 E-GIST and 38 E-LMS patients, with esophagectomy and systemic treatment rate of 55% and 49% for E-GIST and 50% and 26% for E-LMS. The 5-year OS of E-GIST and E-LMS were 62% and 23%, respectively, $p < 0.001$. In multivariable analysis, young age, tumor <10 cm, esophagectomy, and E-GIST were associated with superior OS. There was a higher median and mean OS with neoadjuvant vs. upfront surgery for E-GIST group (98 and 111 vs 79 and 80 months).
Conclusion: E E-GIST has superior OS compared to E-LMS. Esophagectomy is the cornerstone treatment modality. Further studies are needed to evaluate the role of neoadjuvant therapy in E-GIST patients.

Introduction

Esophageal malignant mesenchymal tumors are rare entities, they account for 0.1–2.8% of all primary esophageal sarcoma (ES).[1,2] Esophageal gastrointestinal stromal tumor (E-GIST) and leiomyosarcoma (E-LMS) comprise the vast majority of these tumors (66%–74% of total primary ES).[2,3] Due to the scarcity of these two malignancies, their clinicopathological features and clinical outcomes were best studied as case series reports[4–7] or else as a subgroup in larger studies including other gastrointestinal locations.[8–10] Other than a published systematic review,[5] the largest ES report included 41 E-GIST and 48 E-LMS patients using the Surveillance, Epidemiology, and End Results (SEER) 1973–2011 Registry.[2] In 2007, Blum et al. reported a National Cancer Database (NCDB) study including a 33 E-GIST diagnosed from 1989 to 2004.[4] These reports included mostly patients from old registries (i.e. prior 2000s).[2,4]

E-GIST were previously misclassified as E-LMS, until gain of function mutations in the KIT receptor tyrosine kinase were described, and subsequently came to define the tumor. Furthermore, GISTs were found to derive from Cajal cells, and an absence of desmin on immunohistochemistry helped delineate them from their smooth muscle counterparts.[11] The advent of tyrosine kinase inhibitors in the early 2000s reformed the way E-GISTs were approached. Specifically, neoadjuvant imatinib has been a particularly beneficial treatment strategy for E-GIST given its anatomically challenging location.[12]

Our aim was to explore the clinicopathological features and outcomes of both E-GIST and E-LMS during the last two decades of in view of the widespread use of the immunohistochemistry and settlement of the historical misclassification.

* Corresponding author.
E-mail address: basemazab5@gmail.com (B. Azab).

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Methods

Data source and selection criteria

Data were obtained from NCDB Participant User File (PUF) for esophageal tumors diagnosed between 2004 and 2014. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It comprises hospital-based registry from more than 1500 commission-accredited cancer programs, encompassing over 70% of all cancer cases in the United States. This study was reviewed as exempt by the local Institutional Review Board at the University of Miami Miller School of Medicine. The study population was based on International Classification of Disease for Oncology (3rd edition) histology code (ICD-O-3) and tumor behavior data (3 = invasive). The patient with E-GIST and E-LMS were defined as those with ICD-O-3 of 8936 and 8890 with invasive behavior tumor, respectively.

Patient demographics, tumor and treatment variables

Potentially relevant demographic (year of diagnosis, age and gender), tumor (location, diameter in cm and tumor grade), and treatment characteristics (surgery and systemic treatment) were included. The tumor location was defined according to ICD-O-3 disease site code: 150 and 153 for upper, 151 and 153 for mid, 152 and 155 for lower esophagus. For statistical consideration, high grade tumor was defined as both grade 3 and 4. The year of diagnosis was studied as continuous variable and was also divided into two categories (2004–2009) and (2010–2014). The esophagectomy approached was identified by codes 20 to 80. The intervals between diagnosis and treatment modalities (esophagectomy and systemic treatment) were reported in days.

Statistical analysis

Continuous variables are presented as mean ± standard error and categorical variables as frequencies and percentages. For group comparisons, Chi-square and Fisher's exact tests were used for categorical variables; ANOVA test was used for continuous variables. Kaplan Meier Curve (KMC) survival estimates and a log-rank test were used to examine differences in OS between E-GIST and E-LMS. Univariate screening individual cox regression analyses were used to examine the association between each variable and OS. Cox regression multivariate analysis was used to identify independent factors associated with OS. All probabilities were two-sided, and p-values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

A total of 141 and 38 patients with E-GIST and E-LMS were identified. The patients with E-GIST had a mean age of 66 year, 54% and 77% of them were male and White, respectively. The patients with E-LMS had no significant difference in their demographic variables form E-GIST patients. The rates of E-GIST and E-LMS were significantly impacted by the year of diagnosis. During 2004–2005, 2006–2007, 2008–2009 and 2010–2011, the rate of E-GIST was 66%, 74%, 75%, 88% and 89% and the rate of E-LMS was 35%, 26%, 24%, 12% and 11%, respectively (Fig. 1). In comparison to those diagnosed between 2004 and 2009, the patients diagnosed between 2010 and 2014 had a statistically significant rise of number of E-GIST (45% vs 55%) and decline of E-LMS (66% vs 34%). The lower third/distal esophagus harbors 71% and 59% of E-GIST and E-LMS, respectively. There was no difference in the tumor size between E-GIST and E-LMS with a maximum diameter mean of 6 cm. Moreover, the rate of high tumor grade was significantly higher in E-LMS compared to E-GIST (81% vs. 48%, p = 0.02. The rate of esophagectomy was 55% among E-GIST and 50% for E-LMS. There was a statistically significant higher rate of systemic treatment among E-GIST (49%) compared to E-LMS (49% vs 26%, p = 0.01). The rate of neoadjuvant systemic treatment was also higher among E-GIST (33% vs 19%, p = 0.08) (Table 1). Likewise, the interval between diagnosis to definitive surgery was significantly longer among E-GIST (mean: 77 vs. 42 days, p = 0.03). There were 22 patients who underwent local excision with available survival data (20 E-GIST and 2 E-LMS) with one E-GIST patient expired within 90-day postoperatively. The 90-day postoperative mortality rate among the esophagectomy patients not coded as local excision were 4/43 (9%) for E-GIST and 2/13 (15%) for E-LMS group with no statistical significant difference (p = 0.6). There was a higher rate of radiotherapy among E-LMS compared to E-GIST patients (12/39 vs 3/141, p < 0.0001). There were only 9 patients with E-LMS who received radiotherapy with available survival data.

Overall survival

Among the patients with known survival status (119 E-GIST and 32 E-LMS), there were 39 and 24 deaths for E-GIST and E-LMS, respectively. The Kaplan Meier survival analysis showed that the mean and median survival of E-GIST were superior to E-LMS (85 and 97 months vs. 39 and 16 months, log rank p < 0.0001) (Fig. 2). The 3-year and 5-year OS of E-GIST were 78% and 62% compared to E-LMS (31% and 23%, respectively). Categorization of E-GIST and E-LMS by their surgical treatment status resulted in 4 groups [group 1 = E-GIST patients who had esophagectomy, 2 = E-GIST patients who had no surgery, 3 = E-LMS patients who had esophagectomy and 4 = E-LMS patients who had no surgery. The Kaplan Meier survival analysis showed that the mean and median survival were the following: group 1 (91 and 110 months), group 2 (75 and 72 months), group 3 (68 and 61 months) and group 4 (12 and 6 months), with Log rank p < 0.0001 (Fig. 3). According to the screening univariate Cox regression, E-LMS had worse OS than E-GIST (HR 3.1, CI 1.83–5.11, p < 0.001). Those who underwent esophagectomy had better OS (HR 0.4, CI 0.3–0.7, p < 0.001). Additionally, univariate analysis demonstrated poor survival with advanced age and tumor size >10 cm. The univariate screening Cox regression models showed that the gender, race, year of diagnosis,

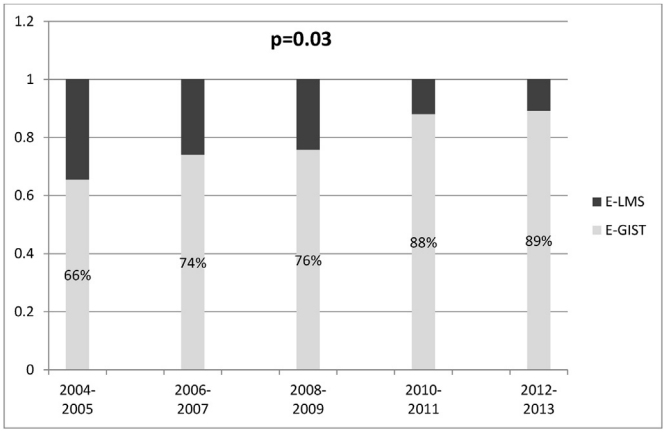

Fig. 1. The rate of esophageal GastroIntestinal stromal tumor (E-GIST) and Leiomysarcoma (E-LMS) according to the year of diagnosis.

Table 1
Baseline characteristics of esophageal GIST and LMS patients.

Baseline characteristics	GIST	LMS	P-Value
	N = 141	N = 38	
Demographic characteristics			
Age (years, Mean & SD)	66.1 ± 12.3	64.7 ± 11.9	0.8
Gender (Males)	76(54%)	23(61%)	0.5
Race(White)	108(77%)	25(66%)	0.2
Diagnosis (2004–2009)	64/141(45%)	25/38(66%)	**0.03**
Diagnosis (2010–2014)	77/141(55%)	13/38(34%)	
Cancer characteristics (N, %)			
Tumor in mid-esophagus	24/104(23%)	9/29(31%)	0.4
Tumor in lower esophagus	74/104(71%)	17/29(59%)	0.4
Tumor size (cm)	6.2 ± 3.9	6.1 ± 3.9	0.8
Tumor size 5–9.9 cm	45/124 (36%)	12/31 (39%)	0.9
Tumor size ≥ 10 cm	23/124 (19%)	6/31 (19%	0.9
Tumor grade (High)	19/40 (48%)	17/21 (81%)	**0.02**
Treatment characteristics and outcomes			
Esophagectomy	78/141(55%)	19/38(50%)	0.6
Systemic therapy	66/134(49%)	9/35(26%)	**0.01**
Diagnosis to surgery interval (days,mean, sd)	77 ± 11.1	42 ± 10.3	**0.03**
Diagnosis to systemic treatment interval (days, mean, se)	70 ± 9.5	50 ± 9.5	0.1
Neoadjuvant systemic treatment	13/39 (33%)	1/12(8%)	0.08

tumor grade, tumor location and systemic treatment were not predictors of OS (Table 2). The multivariate Cox regression showed that increase age per year (HR 1.1, 95% CI 1.03–1.10, $p < 0.001$), tumor size >10 cm (HR 2.6, 95% CI 1.25–5.45, $p = 0.01$), esophagectomy (HR 0.5, 95% CI 0.25–0.95, $p = 0.03$) and E-LMS vs E-GIST (HR 5.0, 95% CI 2.41–10.42, $p < 0.001$) were significant predictors of mortality (Table 2).

Further subgroup analysis of E-GIST patients who underwent esophagectomies was performed with known sequence of surgical and systemic treatments and survival status. There were 12 and 20 patients who had neoadjuvant and upfront surgery, respectively. We observed a higher median and mean survival time (98 and 111 months) for neoadjuvant group vs. those had upfront surgery (79 and 80 months). However, OS was not statistically different between the upfront surgery and neoadjuvant groups of E-GIST.

Discussion

To our knowledge, our study includes the largest number of E-GIST/E-LMS published to date. The results of our study suggest the following: 1) E-GIST has better overall survival than E-LMS after controlling other variables including surgery, 2) Surgery is the cornerstone treatment in both tumors with survival benefit in both E-GIST and E-LMS, 3) There was a higher rate of systemic treatment and trend of a higher rate of neoadjuvant therapy in E-GIST compared to E-LMS, 4) E-GIST patients with neoadjuvant therapy

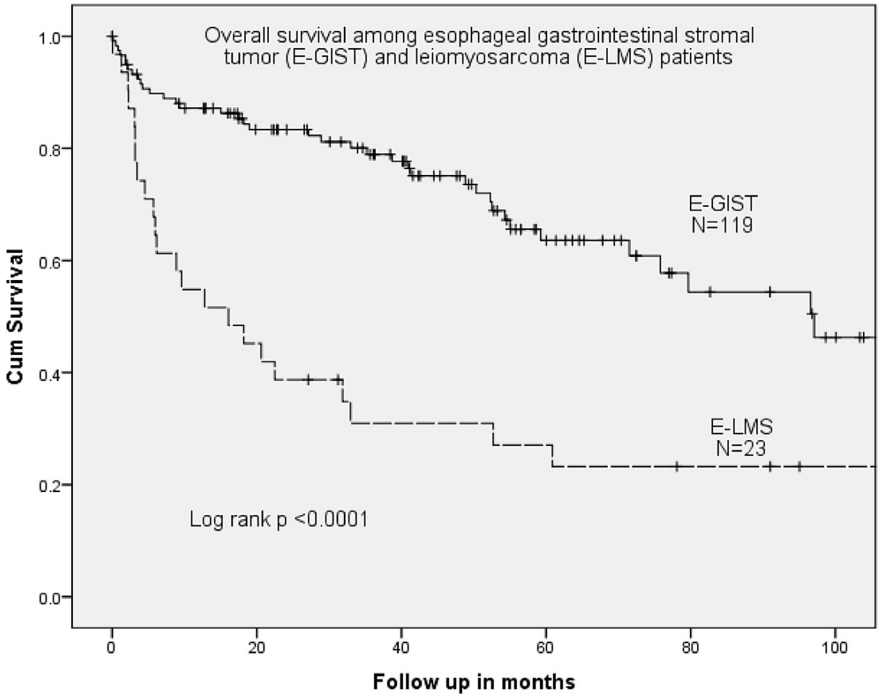

Fig. 2. The Overall Survival among Esophageal GastroIntestinal Stromal Tumor (E-GIST) and Leiomyosarcoma(E-LMS) patients.

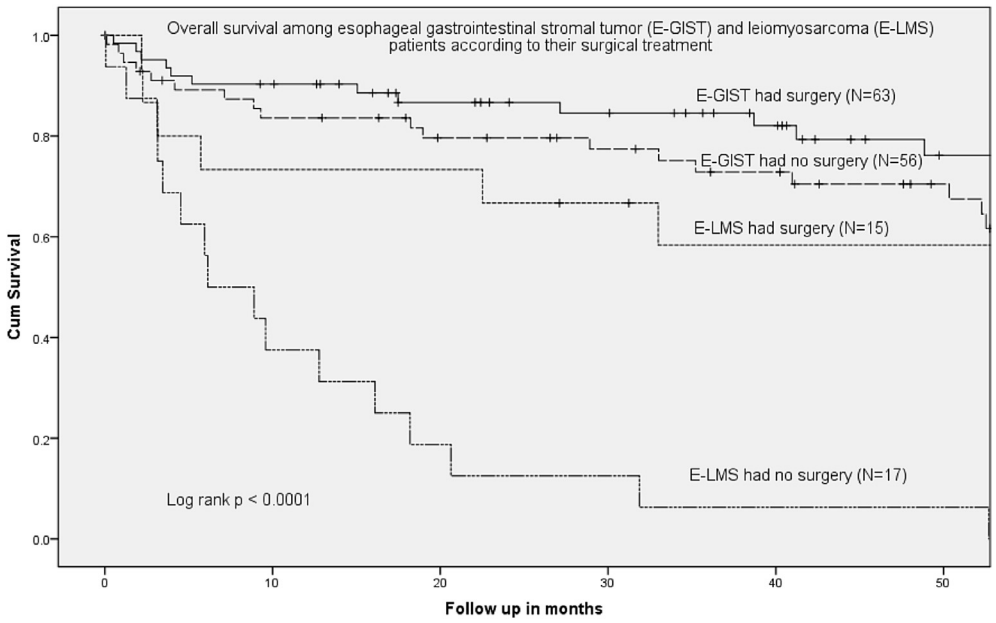

Fig. 3. The Overall Survival among Esophageal GastroIntestinal Stromal Tumor (E-GIST) and Leiomyosarcoma (E-LMS) patients according to their surgical treatment.

had higher median and mean survival than those underwent upfront surgery, however this was not statistically significant, 5) Over the past decade, there is a rising rate of diagnosed E-GIST in conjunction with drop in E-LMS, rate that could be attributed to superior immunohistochemistry techniques and a resolved misclassification dilemma, 6) advanced age and tumors larger than 10 cm in diameter were independent predictors of poor survival.

We demonstrated that E-GIST has an independent superior OS than E-LMS, with higher 3-year and 5-year OS (78% and 63%) among E-GIST compared to the largest prior report of a 55 E-GIST patients (72% and 48%).[13] Likewise, our results corroborate that of Wu et al. (SEER data base study) about the superior survival of E-GIST compared to E-LMS (5-year OS: 77% and 30%, respectively).[2] Furthermore, the long term results of an early adjuvant imatinib trial, including mostly gastric and enteric GIST, reported a 3- and 5-year OS of 97% and 83%, respectively.[14] Of note, these OS rates of GIST are remarkably superior to the historical 5-year OS of 28–35% of the pre-imatinib era.[15,16] On the other hand, our current results showed lower E-LMS OS rates than those reported prior 2000s. In 1992, Ng et al. reported 28% 5-year OS for the gastrointestinal LMS,[16] which is higher than our current study with E-LMS 5-year OS of 23%. This observation is likely because of prior inclusion of E-GIST patients with better OS survival under E-LMS categorization. Now that those patients are properly classified as E-GIST with the considerable development of tyrosine kinases inhibitors and effective systemic therapy for them[17,18]; the real, now isolated, E-LMS poor overall survival rates are observed, especially with little advancement in its systemic therapy.

While the survival advantage of esophagectomy patients could be a surrogate to better performance status and less tumor burden, the E-LMS continued to have poor survival even after esophagectomy in comparison to E-GIST. Furthermore, we found a modest higher mean and median survival time of E-GIST patient who had no surgical resection than E-LMS patients who had esophagectomy. Interestingly, our results demonstrated the independent positive impact of esophagectomy on OS among both E-GIST and E-LMS patients, while systemic treatment did not. This concurs with prior published literature suggesting surgical resection as the cornerstone treatment of E-GIST and E-LMS.[2,4] Conversely, Wu et al. showed better survival with esophagectomy in E-LMS but not E-GIST; this can be attributed to the small number of E-GIST (only 26 patients) included in that study.[2]

Table 2
Cox regression analyses for Predictors of Mortality among Esophageal Gastrointestinal Stromal Tumor and Leiomyosarcoma Patients.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-Value	HR (95%CI)	P-Value
Age (per year)	1.07 (1.04–1.10)	**0.001**	1.1 (1.03–1.10)	**0.001**
Sex (male)	1.4 (0.87–2.40)	0.2		
Race (Caucasian)	1.2 (0.70–2.10)	0.5		
Year of diagnosis (Ref: 2004–2009)	0.8 (0.42–1.37)	0.36		
Tumor location (Ref: lower)				
Upper esophagus	1.6 (0.57–4.73)	0.35		
Mid esophagus	1.2 (0.59–2.31)	0.66		
Tumor size				
Tumor size 5–9.9 cm (Ref <5 cm)	0.8 (0.42–1.62)	0.6		
Tumor ≥ 10 cm (Ref <5 cm)	2.2 (1.14–4.42)	**0.02**	2.6 (1.25–5.45)	**0.01**
Tumor grade (high)	2.1 (0.77–5.72)	0.2		
Esophagectomy	0.4 (0.26–0.72)	**0.001**	0.5 (0.25–0.95)	**0.03**
Systemic treatment	1.0 (0.59–1.65)	0.9		
E-GIST vs. E-LMS	3.1 (1.83–5.11)	**0.001**	5.0 (2.41–10.42)	**0.001**

Of note, Lott et al. described the superior 3- and 5-year OS in gastric GIST (85% and 77%) compared to E-GIST (72% and 48%).[13] This survival difference could be attributed to both anatomical and biological factors. While esophagectomies are considered morbid procedures, most gastric GIST and LMS resections entail just partial or sleeve gasterectomies. Moreover, previous reports showed higher rate of wild type, higher mitotic figures and high-risk GIST in E-GIST compared to gastric GIST.[13,19]

Though we found higher mean and median survival among E-GIST patients with neoadjuvant therapy vs. those with upfront surgery, the number of the patients was too small to reach statistical significance. Interestingly, both E-GIST and E-LMS had comparable tumor size with (mean tumor diameter = 6 cm for both, $p = 0.8$), but there was a higher systemic treatment rate and neoadjuvant therapy among E-GIST (49% and 33%) vs. E-LMS (26% and 8%). This reflects the widespread acceptance/tolerance of the neoadjuvant approach among E-GIST in comparison to E-LMS. In study including GIST of various anatomical sites, Rutkowski et al. reported excellent outcomes with neoadjuvant imatinib therapy for locally advanced GIST (5-year OS = 95% and R0 resection of 83%).[12] We speculate that the neoadjuvant therapy of E-GIST will decrease the potential of tumor rupture and improve R0 resection rate for these anatomically challenging procedures, especially in tumors with favorable genetic mutations (e.g. exon 11 mutations).

There was a significant reciprocal change of the rate of E-GIST and E-LMS through the reported years (2004–2014) that suggest a correction of a prior misclassification. However, there is to some extent a steady rate for both diseases after 2010. These findings could be attributed the historical evolution of pathological immunohistochemistry (IHC) as a pivotal role in identification of GIST. In 1983, Mazur and Clark were the first to report the gastric stromal as a distinguished entity that should not be classified as nerve sheath or smooth muscle tumors.[20] However, differentiation of the smooth muscle tumors from GIST remained a pathological challenge until further tumor definitions based on their IHC profile were adopted. In 2001, Miettinen et al. defined the GIST as the primary gut tract mesenchymal tumors with positive tyrosine-protein kinase (KIT) receptor (also known as CD117) with approximately 70% of these tumors stained positive for CD34.[11] They all also reported the possible IHC staining of GIST tumors with smooth muscle tumor and neurogenic tumors markers (20–30% GIST were positive for smooth muscle actin (SMA), <5% GIST were positive for desmin and 10% were positive for S100 protein).[11] Further IHC markers, platelet derived growth factor receptor alpha (PDGFRA) and a later Discovered On-GIST 1 (DOG-1) antibody, were developed to identify the non-mutated KIT GIST (also known as Wild type GIST). In 2004, West et al. demonstrated the ubiquitous expression of DOG-1 marker in GIST irrespective of their KIT or PDGFRA mutation status,[21] however later recognition of the limitations of both KIT and DOG-1 was illustrated by Miettinen et al., in 2009.[22]

The baseline characteristic of our study showed no gender predilection (i.e. 54% of E-GIST were males), contrary to prior reports of male predominance.[13,19,23] The negative impact of advanced age[2] and tumor size >10 cm, were not surprising and they similar to data from previous studies.[15,24] The E-GISTs were mostly in lower esophagus (71%), but the number of E-LMS was small to study their location predilection. We speculate that the E-GIST's distal tendency could be attributed to the distribution of interstitial cells of Cajal within the esophageal muscularis as suggested by previous studies.[25,26]

We acknowledge that our study has several limitations. Despite including a relatively large number of patients, the data analyzed is extracted from nationwide registry, which may include potential bias. Our study is also limited by the retrospective nature and the lack of intention to treat analysis. The limited number of patients underwent radiotherapy and local excision precluded sub-analyses to evaluate the impact of these modalities on survival. The NCDB does not have records about the mutation analysis of these tumors, which are currently an integral tool to direct the treatment for GIST. Nevertheless, the current study provides the largest series of E-GIST and E-LMS to date.

Conclusion

In this study, we found a rising rate of diagnosed E-GIST in conjunction with a declining rate of diagnosed E-LMS over the past decade. E-GIST had better OS than E-LMS after controlling for confounding factors. Surgical resection is the cornerstone treatment for both entities. We also showed a higher rate of systemic treatment, including neoadjuvant therapy in E-GIST. Further studies assessing the role of the neoadjuvant therapy in E-GIST and the introduction of more effective systemic therapies for E-LMS are warranted.

References

1. Perch SJ, Soffen EM, Whittington R, Brooks JJ. Esophageal sarcomas. *J Surg Oncol*. 1991;48:194–198.
2. Wu GX, Ituarte PH, Paz IB, Kim J, Raz DJ, Kim JY. A population-based examination of the surgical outcomes for patients with esophageal sarcoma. *Ann Surg Oncol*. 2015 Dec;22(Suppl 3):S1310–S1317.
3. Saddoughi SA, Taswell J, Harmsen WS, et al. Surgical resection of rare esophageal cancers. *Ann Thorac Surg*. 2016 Jan;101(1):311–315.
4. Blum MG, Bilimoria KY, Wayne JD, de Hoyos AL, Talamonti MS, Adley B. Surgical considerations for the management and resection of esophageal gastrointestinal stromal tumors. *Ann Thorac Surg*. 2007;84:1717–1723.
5. Pence K, Correa AM, Chan E, Khaitan P, Hofstetter W, Kim MP. Management of esophageal gastrointestinal stromal tumor: review of one hundred seven patients. *Dis Esophagus*. 2017 Dec 1;30(12):1–5.
6. Winant AJ, Gollub MJ, Shia J, Antonescu C, Bains MS, Levine MS. Imaging and clinicopathologic features of esophageal gastrointestinal stromal tumors. *AJR Am J Roentgenol*. 2014 Aug;203(2):306–314. https://doi.org/10.2214/AJR.13.11841.
7. Zhang BH, Zhang HT, Wang YG. Esophageal leiomyosarcoma: clinical analysis and surgical treatment of 12 cases. *Dis Esophagus*. 2014;27:547–551.
8. Kukar M, Kapil A, Papenfuss W, Groman A, Grobmyer SR, Hochwald SN. Gastrointestinal stromal tumors (GISTs) at uncommon locations: a large population-based analysis. *J Surg Oncol*. 2015;111(6):696–701.
9. Perez EA, Gutierrez JC, Jin X, et al. Surgical outcomes of gastrointestinal sarcoma including gastrointestinal stromal tumors: a population-based examination. *J Gastrointest Surg*. 2007;11:114–125.
10. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1458 cases from 1992 to 2000. *Am J Gastroenterol*. 2005;100:162–168.
11. Miettinen M, Lasota J. Gastrointestinal stromal tumors–definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch*. 2001 Jan;438(1):1–12.
12. Rutkowski P, Gronchi A, Hohenberger P, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. *Ann Surg Oncol*. 2013 Sep;20(9):2937–2943. https://doi.org/10.1245/s10434-013-3013-7.
13. Lott S, Schmieder M, Mayer B, et al. Gastrointestinal stromal tumors of the esophagus: evaluation of a pooled case series regarding clinicopathological features and clinical outcome. *Am J Cancer Res*. 2014 Dec 15;5(1):333–343.
14. DeMatteo RP, Ballman KV, Antonescu CR, et al. American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team for the Alliance for Clinical Trials in Oncology. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. *Ann Surg*. 2013 Sep;258(3):422–429.
15. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg*. Jan; 2000;231(1):51–58 [PubMed: 10636102].
16. Ng EH, Pollock RE, Munsell MF, et al. Prognostic factors influencing survival in gastrointestinal leiomyosarcomas. Implications for surgical management and staging. *Ann Surg*. Jan; 1992;215(1):68–77.
17. Dematteo RP, Ballman KV, Antonescu CR, et al. American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009 Mar 28;373(9669):1097–1104. https://doi.org/10.1016/S0140-6736(09)60500-6.
18. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *J Am*

Med Assoc. 2012 Mar 28;307(12):1265–1272. https://doi.org/10.1001/jama.2012.347.
19. Jiang P, Jiao Z, Han B, et al. Clinical characteristics and surgical treatment of oesophageal gastrointestinal stromal tumours. *Eur J Cardio Thorac Surg*. 2010;38:223–227.
20. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. *Am J Surg Pathol*. 1983 Sep;7(6):507–519.
21. West RB, Corless CL, Chen X, et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. *Am J Pathol*. 2004 Jul;165(1):107–113.
22. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. *Am J Surg Pathol*. 2009 Sep;33(9):1401–1408. https://doi.org/10.1097/PAS.0b013e3181a90e1a.
23. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leio-myosarcomas. *Am J Surg Pathol*. 2000;24:211–222.
24. Clary BM, DeMatteo RP, Lewis JJ, Leung D, Brennan MF. Gastrointestinal stromal tumors and leiomyosarcoma of the abdomen and retroperitoneum: a clinical comparison. *Ann Surg Oncol*. 2001 May;8(4):290–299.
25. Berezin I, Daniel EE, Huizinga JD. Ultrastructure of interstitial cells of cajal in the canine distal esophagus. *Can J Physiol Pharmacol*. 1994;72:1049–1059.
26. JD1 Huizinga, Chen JH, Mikkelsen HB, et al. Interstitial cells of Cajal, from structure to function. *Front Neurosci*. 2013 Apr 1;7:43.