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Endoscopic resection for esophageal granular cell tumors: report of 62 cases

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Abstract

Background To analyze the clinical manifestations, endoscopic features, pathological features, endoscopic resection, and prognosis of esophageal granular cell tumors (GCTs).

Methods The present study retrospectively analyzed and followed up the clinical data of 62 patients diagnosed with esophageal GCTs who underwent endoscopic resection at Zhongshan Hospital of Fudan University between July 2007 and March 2022. The clinicopathological features, endoscopic diagnosis, and treatment experience of esophageal GCT patients were summarized.

Results Among the 62 patients with esophageal GCT, there were 34 males and 28 females, with an average age of 49.3 ± 11.7 years. Only 11 patients had symptoms, such as epigastric discomfort, regurgitation or dysphagia. One patient had multiple lesions, and the rest had single lesions, totaling 63 lesions. Most lesions (53/63) were located in the median and lower esophagus, the diameters ranged from 3 to 22 mm. The endoscopic morphology of the GCTs was molar, flat, hemispherical, or irregular submucosal protuberance. Endoscopic ultrasound (EUS) was performed in 38 cases, most cases (31/38) were hypoechoic, and 32 cases were appeared as homogeneous lesions. There were no complications during or after the endoscopic operations, and the en bloc resection rate was 100%. The negative rate of microscopic incisional margin was 63.5% (40/63). No patients developed recurrence during the follow-up period. The follow-up duration was 21–197 months (100.5 months for average).

Conclusion Esophageal GCT is a rare disease with no obvious symptoms and a good prognosis. Endoscopic resection is a safe and effective method of diagnosis and treatment for esophageal GCTs. A microscopic positive tumor margin may not increase the rate of recurrence.

Keywords Esophageal granular cell tumors, Clinical manifestation, Endoscopic features, Endoscopic resection

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Introduction

Granular cell tumors (GCTs) are rare soft tissue tumors that were first reported by Abrikossoff in 1926 [1]. GCTs were named for the uniform distribution of eosinophilic particles in the cytoplasm. At present, GCTs are believed to originate from Schwann cells in the peripheral nerve sheath; most of them are benign, and few of them have a malignant tendency to metastasize [2]. GCTs can occur in different organs, such as the tongue, skin, and subcutaneous tissue, and only approximately 10% of GCTs occur in the gastrointestinal tract, most commonly in the esophagus [3]. In recent years, with the popularization of endoscopy, the detection rate of esophageal GCTs has gradually increased, which has attracted attention because of its malignant potential. The vast majority of esophageal GCTs are benign, but a few of them can occasionally grow during follow-up, show invasion into the muscular propria, or metastases of lung and liver. Some scholars do not advocate the resection of GCTs, if the diagnosis is clear. However, in many cases, the nature of submucosal tumors is difficult to diagnose. Thus, endoscopic resection is a viable option, provided that endoscopic resection techniques allow.

In the present study, we retrospectively analyzed 62 patients with esophageal GCTs who had undergone endoscopic resection in our center in the past 15 years. We attempted to summarize the clinicopathological characteristics and evaluate the efficacy and safety of endoscopic resection for esophageal GCTs.

Methods

Patient selection

This is a single-center, retrospective study. Through searching pathological databases, 67 patients who underwent endoscopic resection of esophageal tumors at Zhongshan Hospital of Fudan University were pathologically diagnosed with GCTs from July 2007 to March 2022. Among them, 5 patients were lost to follow-up, and the other 62 patients had a complete medical history. The clinical characteristics, endoscopic manifestations, surgical methods, and pathological characteristics of the patients were collected. The study was approved by the ethics committee of Zhongshan Hospital of Fudan University (No.B2023-279).

Intervention

All patients underwent endoscopic therapy under general anesthesia, and vital signs were monitored during the operation. All procedures were performed by experienced endoscopic physicians. The operation modes included snare excision, endoscopic submucosal dissection (ESD), and submucosal tunneling endoscopic resection (STER). The treatment strategies depended on the size and the depth of infiltration of the esophageal wall and also on local expertise. In cases where endoscopic ultrasound (EUS) suggested the lesion originated from the mucosal muscle or submucosal layer, snare excision or ESD was selected, whereas for esophageal lesions suspected to originate from the muscularis propria layer, STER was chosen. For the patients without preoperative EUS, ESD was conducted.

The therapy-related complications were recorded, including intraoperative bleeding, postoperative bleeding, intraoperative perforation, postoperative perforation, postoperative infection, etc.

Histologic evaluation

Postoperative specimens were fixed with formaldehyde, embedded in paraffin, and then sectioned consecutively for HE staining. The expression of S-100 protein, NSE, Nestin, CD68, CD34, CD117, SMA, Desmin, DOG-1, and Ki-67 was detected by immunohistochemistry in 55 specimens. Under the microscope, no tumor cells were found at the vertical and basal margins of the specimen, which was defined as a microscopic negative tumor margin. Tumor tissue with burning degeneration or no normal tissue under the microscope was defined as a microscopic positive tumor margin.

Follow-up

All patients underwent clinical follow-up. Wound healing was reviewed endoscopically at the 1st and 6th months after surgery to observe any residual or recurrence, followed by gastroscopy once a year or every two years thereafter. For patients from distant provinces and those unwilling to come back for follow-up, detailed telephone interviews, including asking about symptoms and treatments or tests received at other hospitals were conducted. The deadline for follow-up was December 31, 2023.

Statistical analysis

All of the statistical analyses were performed using the Excel software package. The enumeration data conforming to a normal distribution are described as the mean ± SD, and the measurement data are described as the frequency (composition ratio).

Results

Patient characteristics

Of the 62 patients, 34 were male and 28 were female. The patients were 25–75 years old, with a mean age of 49.3 ± 11.7 years. Eleven patients had clinical symptoms: six of them showed epigastric discomfort, four showed acid reflux and heartburn, one showed choking on food, and the remaining 51 patients had no obvious discomfort that was found during physical examination. An overview

of patient background characteristics and procedures is summarized in Table 1.

Endoscopic and EUS performance

One patient had two lesions, and the rest had single lesions, for a total of 63 lesions. Ten of the lesions were located in the upper esophagus, 21 in the middle esophagus, and 32 in the lower esophagus. The maximum diameter of the lesions was 3–22 mm, with a mean of (8.7±4.8) mm. The endoscopic morphology of GCTs was molar-like, flat, irregular or hemispheric bulge, with a yellowish or gray appearance (Fig. 1a, e, i). Most of them were firm and failed to demonstrate a pillow sign. Intriguingly, according to the postoperative pathological results, we discovered that the lesions with endoscopic morphology of hemispheric bulge, especially the diameter of the lesion > 10 mm, are more likely to be originated from the muscularis propria layer (3/4), and the lesions with molar-like appearance are all originated from muscularis mucosa layer or submucosa layer (17/17).

Table 1 Characteristics of 62 GCT patients (63 lesions)

Clinical characteristics	*n*	%
Gender		
Male	34	54.8
Female	28	45.2
Age(year)		
25–39	15	24.2
40–59	36	58.1
60–75	11	17.7
Symptoms		
Epigastric discomfort	6	9.7
Regurgitation and heartburn	4	6.5
Dysphagia	1	1.6
None	51	82.3
Location		
Upper	10	15.9
Middle	21	33.3
Lower	32	50.8
Maximum diameter (mm)		
≤ 5	21	33.3
6–9	22	34.9
10–19	16	25.4
≥ 20	4	6.3
Color		
yellow	40	63.5
gray	23	36.5
Endoscopic morphology		
Molar-like	17	27
Flat	17	27
Irregular bulge	11	17.5
Hemispheric bulge	18	28.6
Therapeutic methods		
Remove by biopsy	1	1.6
Snare excision	3	4.8
ESD	52	82.5
STER	7	11.1
Pathological cutting edge		
R1	23	36.5
R0	40	63.5

Preoperative EUS was completed in 38 patients. For echoes, 4 cases were hyperechoic, 3 cases were moderately echogenic, 31 cases were hypoechoic; 32 cases were homogeneous and 6 cases were heterogeneous. Regarding origins, 17 lesions originated from the mucosal muscle layer, 14 from the submucosal layer, and 7 from the muscularis propria layer (Table 2; Fig. 1b, f, j). According to the postoperative pathological results, the accuracy rate of preoperative EUS depth was 94.7% (36/38). Two lesions with irregular morphology which were suspected to originate from the submucosal layer with preoperative EUS, were observed local adhesion to the muscularis propria layer in the operation, and the lesions were verified to be originated from the muscularis propria layer by postoperative pathological results.

Treatment procedures

One lesion was biopsy occluded, three superficial lesions originating from the mucosal muscle layer were resected by snare excision (Fig. 2a-d), 52 lesions originating from the mucosal muscle or submucosal layer were resected by ESD (Fig. 2e-h), and seven lesions originating from the muscularis propria layer were resected by STER (Fig. 2i-l). All lesions were excised completely with no residual endoscopic findings. No complications such as bleeding, perforation, or infection occurred in any patients during the perioperative period.

Pathological and immunohistochemical features

The grossly observed masses had no obvious envelopes, and the cut surfaces were grayish yellow or grayish white. The tumor cells were polygonal or ovoid, arranged into nests or sheets, with abundant cytoplasm, and contained a large number of eosinophilic fine particles. The cell nuclei were small and round, with no nuclear division (Fig. 1c, g, k).

Immunohistochemistry was performed in 55 lesions. The results showed that all tumor cells were positive for S-100 protein (Fig. 1d, h, l), and were partially positive for NSE, Nestin, and CD68. However, all samples were negative for CD34, CD117, SMA, desmin or DOG-1. One lesion with the largest volume (maximum diameter 22 mm) was 10% positive for Ki-67, and the rest of the lesions were less than 5% positive for Ki-67. No tumor cells were observed on the vertical and basal margins of the specimens under the microscope in 40 cases, cauterized degenerative tumor tissue was observed on the margins of the specimens in 10 cases, and no normal tissue was observed on the local margins in 13 cases. The

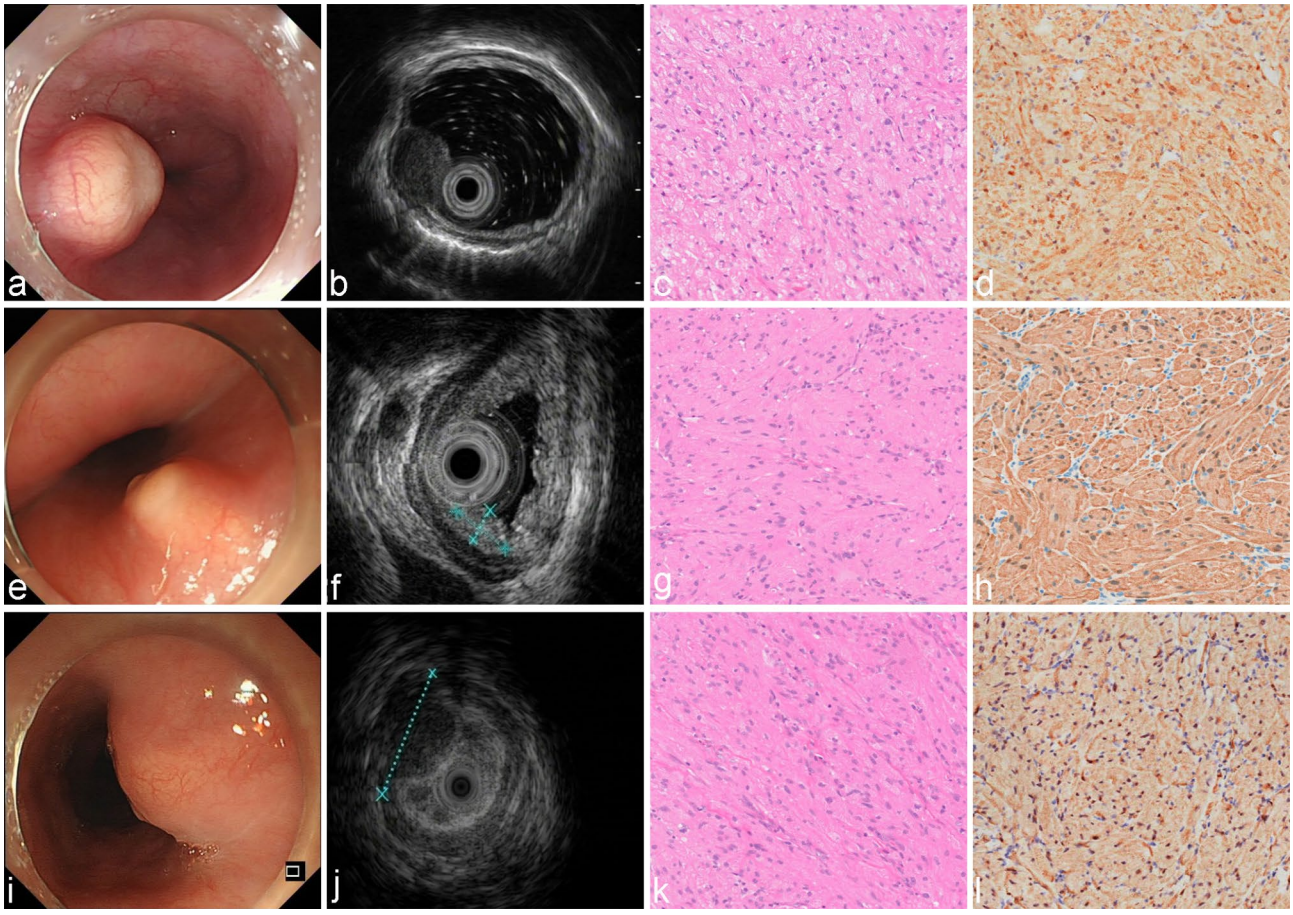

Fig. 1 Endoscopic and pathological features of esophageal GCTs. (**a**) Endoscopic manifestation of an esophageal GCT originating from the mucosal muscle layer. (**b**) Hypoechoic occupancy of the mucosal muscle seen by EUS. (**c**) HE staining (×400). (**d**) Immunohistochemistry of S-100 protein (×400). (**e**) Endoscopic manifestation of an esophageal GCT originating from the submucosal layer. (**f**) Medium echoic occupancy of the submucosal layer seen by EUS. (**g**) HE staining (×400). (**h**) Immunohistochemistry of S-100 protein (×400). (**i**) Endoscopic manifestation of esophageal GCT originating from the muscularis propria. (**j**) Hypoechoic occupancy of the muscularis propria seen by EUS. (**k**) HE staining (×400). (**l**) Immunohistochemistry of S-100 protein (×400)

Table 2 EUS features of the 38 esophageal GCTs

EUS features	*n*	%
EUS echo		
hyperechoic	4	10.5
medium echoic	3	7.9
hypoechoic	31	81.6
Echo characteristics		
homogeneous	32	84.2
heterogeneous	6	15.8
EUS depth*		
mm	17	44.7
sm	14	36.8
mp	7	18.4

* mm, originated from the muscularis mucosa layer; sm, originated from the submucosal layer; mp, originated from the muscularis propria layer

EUS, endoscopic ultrasound

negative rate of the margins under the microscope was 63.5% (40/63).

Follow-up results

All patients were followed up for more than 12 months. The average follow-up period was 100.5 months. At 21–197 months postoperative follow-up, all patients had completed at least two endoscopic reviews, and none had recurrence during the follow-up period.

Discussion

Esophageal GCT is clinically rare and can occur at any age. It is more common in middle-aged people aged 40–60 years, and there are slightly more women than men [2]. The age of the patients in this study ranged from 25 to 75 years, with a mean of 49.9 ± 12.4 years, and there was no significant difference in the male to female ratio. Most patients with esophageal GCTs have no clinical symptoms, most GCTs are found incidentally during endoscopy; and a few patients have choking or difficulty

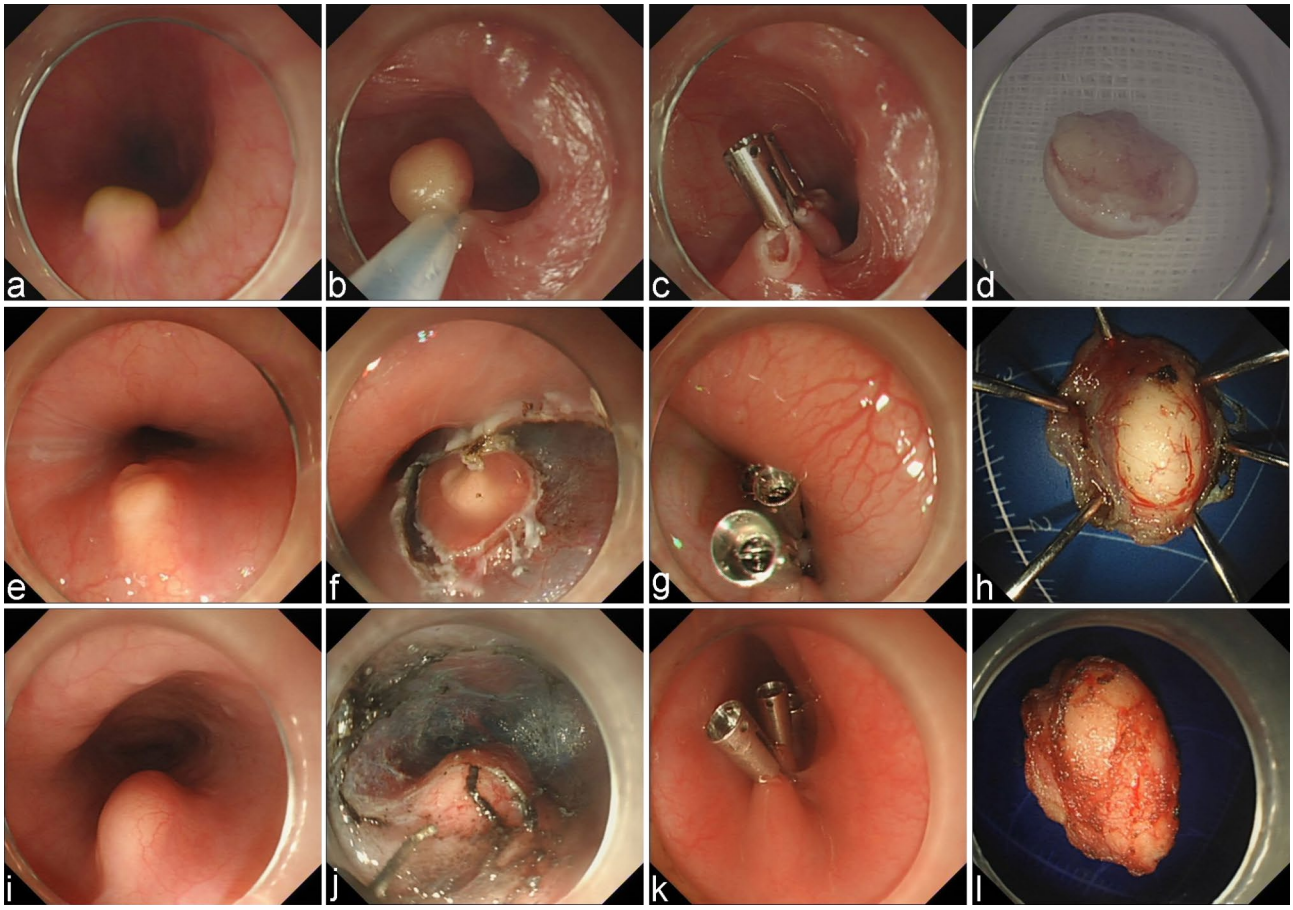

Fig. 2 Endoscopic resection of esophageal GCTs. (**a**) Snare excision of an esophageal GCT. (**b**) Complete electrodissection of the lesion by a snare. (**c**) The wound was closed by metal clips. (**d**) Macroscopic appearance of the resected specimen. (**e**) ESD of an esophageal GCT. (**f**) Submucosal dissection after preincision of the lesion margin. (**g**) The wound was closed by metal clips. (**h**) Macroscopic appearance of the resected specimen. (**i**) STER of an esophageal GCT. (**j**) The lesion originating from the muscularis propria was seen in the submucosal tunnel. (**k**) Closure of the mucosal entry orifice. (**l**) Macroscopic appearance of the resected specimen

swallowing due to an increase in tumor size [4]. It has been reported in the literature that there is an association between esophageal GCTs and reflux esophagitis [5]. In our group, four patients had reflux symptoms and two patients had endoscopic confirmation of reflux esophagitis manifestations. The relationship between the two diseases needs to be further verified because of the small number of cases at present.

GCTs of the esophagus mostly occurred in the middle and lower esophagus, which accounted for 84.1% of cases in this study, similar to previous reports [2]. Morphologically, esophageal GCTs show a yellowish or grayish submucosal elevation, and the most typical form is a slightly depressed central molar-like elevation, probably due to the high affinity between granulosa cells and the esophageal complex squamous epithelium, and the central infiltration of the tumor into the squamous epithelium, resulting in the thinning of the complex squamous epithelium and thus the molar-like form. In 27% (17/63) of our cases, the lesions showed a molar appearance, while the rest showed flat, hemispherical or irregular elevations. The volume of esophageal GCTs was generally small, less than 20 mm in diameter, and the mean diameter of the lesions in this study was 8.7±4.8 mm, with the largest case being 22×15×10 mm. EUS of esophageal GCTs mostly show hypoechoic occupancy with uniform internal echogenicity, mostly originating from the mucosal muscle layer or submucosal layer, and less from the intrinsic muscle layer [6]. In our group, most of the lesions (81.6%) were hypoechoic, mostly with homogeneous echogenicity on EUS (84.2%), mostly originating from the mucosal muscle layer or submucosa (81.6%), and a few originating from the muscularis propria layer (18.4%).

Since GCTs of the esophagus have malignant potential [7, 8], most guides now recommend resection of the growing or symptomatic GCTs after diagnosis, including surgical resection and endoscopic resection [9, 10]. Regarding the indication for endoscopic resection, the guidelines published by the European Society of

Gastrointestinal Endoscopy suggested that tumors with malignant potential (including gastrointestinal mesenchymal tumors, neuroendocrine tumors and, to a lesser extent, GCTs) are indications for endoscopic resection [9]. The Chinese guidelines [10] stated that endoscopic resection should be considered for tumors suspected on preoperative examination or biopsies confirming the presence of malignant potential, provided that endoscopic resection techniques allow. However, the nature of submucosal tumors is difficult to diagnose and only a small number of lesions can be diagnosed by EUS, while most need to be diagnosed via acquisition of tissue for pathological examination. At present, the common methods for obtaining tissues are EUS-guided fine needle biopsy and mucosal excisional biopsy [11], but these methods are technically difficult and economically costly, and sometimes do not allow a sufficient sample size to be obtained. In recent years, with advances in endoscopic treatment, the concept of 'diagnostic resection' has gradually been accepted [12], allowing a complete specimen to be obtained in a single procedure to clarify the diagnosis, while removing the lesion, greatly reducing the financial and psychological burden on the patient. Therefore, for submucosal tumors in the esophagus, if GCTs cannot be excluded from the preoperative diagnosis, endoscopic resection should be chosen when endoscopic resection techniques allow.

The current endoscopic resection methods for GCTs of the esophagus are mainly ESD and endoscopic mucosal resection (EMR) [13–16]. Because ESD has the advantage of complete resection of subepithelial lesions, most of the cases in this study were resected by ESD, and the whole mass was resected. Three cases of superficial lesions originating from the muscularis mucosa layer were resected by snare excision, with a short operative time and complete resection without tumor residue. Seven lesions originating from the muscularis propria layer were resected by STER. The STER technique preserves a safe distance between the mucosal incision and the lesion, and resects the lesion of the muscularis propria layer through the submucosal tunnel. The technique reduces the difficulty of closing the wound endoscopically and minimizes the risk of perforation, gas-related complications and infection. No intraoperative or postoperative complications such as bleeding, perforation, or infection occurred in any cases in this study, and the treatment results were satisfactory, indicating that endoscopic resection of esophageal GCTs is a safe and effective treatment method.

Pathological examination is the gold standard for the diagnosis of GCTs. Microscopically, the tumor cells were round, shuttle-shaped or polygonal, arranged in nests or sheets, with abundant cytoplasm, and uniformly distributed eosinophilic granules. The small, uniformly sized nuclei were centrally located, with rare mitotic nuclear division [17]. Immunohistochemical analysis showed that the tumor cells were positive for the S-100 protein, partially positive for NSE and Nestin, and negative for CD34, CD117, SMA and Desmin [18, 19]. The majority of GCTs were benign lesions, and only approximately 2% had malignant biological behavior. The occurrence of distant metastases could be clearly diagnosed as malignant GCT, but the pathological diagnostic criteria to distinguish benign from malignant are still controversial [7, 20]. In the present study, all 63 lesions were diagnosed as benign, and only one of them had a Ki-67 index of 10%. However, there were no malignant manifestations such as nuclear pleomorphism, increased nucleoplasm ratio, tumor necrosis, or nuclear schizophrenia > 2/10 HPF.

Of interest, 23 cases in this study were determined to have positive microscopic margins (36.5%), but none of the patients showed recurrence during the follow-up. Unlike surgical procedures, several studies have reported that positive microscopic margins are not a risk factor for recurrence after endoscopic resection of submucosal tumors in the gastrointestinal tract [21, 22]. A retrospective analysis of 777 endoscopically resected gastric mesenchymal tumors in our center showed that the rate of positive microscopic margins was as high as 57%, but there was no statistical association between positive microscopic margins and local recurrence of tumors [22]. This may be due to the high delicacy of the endoscopic resection procedure, with electrodesiccation peeling immediately adjacent to the tumor margin, which may predispose to the microscopic observation of localized cut margins where burned degenerated tumor tissue is seen or no normal tissues are seen.

This study had several limitations. First, this was a single-center retrospective study and pathological databases were used to select esophageal GCTs. An unavoidable selection bias existed, although the patients in our center were from different regions of China. Second, the patients were selected for endoscopic resection according to the clinical decisions of the doctors at the time of treatment. Thus, the therapeutic regimen may be influenced by the technical capacity of the physician. Third, unlike gastrointestinal stromal tumors, which have an envelope, GCTs do not have an envelope. Thus, the relationship between the positive microscopic margins and tumor recurrence requires further verification.

Conclusion

Esophageal GCTs are clinically rare and mostly benign. Most patients of esophageal GCTs have no specific symptoms. Endoscopic resection is a appropriate method for obtaining an accurate pathological diagnosis and for treatment, which is safe and effective for esophageal GCTs. Positive microscopic margins may not increase

the risk of tumor recurrence, and patients generally have a good prognosis.

Abbreviations

GCT	Esophageal granular cell tumor
ESD	Endoscopic submucosal dissection
STER	Submucosal tunneling endoscopic resection
EMR	Endoscopic mucosal resection

Author contributions

CG, JC and QJ contributed equally to this work. Conceptualization: PZ and JH. Writing: CG and JC. Data collection: CG, QJ, JW, KG and JN. All authors have read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Zhongshan Hospital of Fudan University (ethics approval number: B2023-279). Due to the retrospective study design, the need for consent to participate was waived by the ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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