Endoscopic Resection of Esophageal Granular Cell Tumors: A Single Center Experience

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Abstract

Background: Granular cell tumors (GCTs) are rare tumors probably originating from neurogenic Schwann cells. The aim was to evaluate the safety and feasibility of endoscopic resection for esophageal GCTs.

Methods: The study retrospectively analyzed patients with pathologically diagnosed esophageal GCTs in our center from February 2012 to December 2020. Clinicopathological characteristics, endoscopic features and clinical outcomes were collected and analyzed.

Results: 12 males and 10 females were identified. Lesions were located in the upper, middle and lower esophagus in three, six and thirteen cases respectively. 14 lesions (63.6%) exhibited white-to-yellow discoloration. The mean maximum diameter of these lesions was 5.7 ± 2.2 mm (range 2-11.6 mm). The most lesions (91%) were located in the mucosa or submucosa layer, and 2 lesions (9.0%) were in the muscularis propria layer. Endoscopic mucosal resection (n=17), endoscopic submucosal dissection (n=4) and endoscopic submucosal excavation (n=1) were performed. En bloc resection was achieved in 20 lesions (90.9%). The R0 resection was achieved in 20 lesions (90.9%). No patients experienced intraoperative perforation or delayed bleeding in the mean length of postoperative hospital stay of 4.2 ± 2.1 days (range 1-9 days). All patients had no recurrence or metastasis during the mean follow-up period of 48.1 ± 27.2 months (range 2-102 months).

Conclusion: Endoscopic resection is safe and effective for management of esophageal GCTs. Clinically, the appropriate approach of endoscopic resection should be selected according to the origin and size of the lesion.

Introduction

Granular cell tumors (GCTs) are rare tumors probably originating from neurogenic Schwann cells [1]. It could occur in nearly all organs, but mostly in the soft tissues, rarely in the gastrointestinal tract [2]. About 8% of all GCTs occur in the gastrointestinal tract, of which 1/3 occur in the esophagus [3]. It is reported that approximately 1–2% of cases are malignant [4–6]. So it is essential to distinguish esophageal GCTs from esophageal submucosal tumors (SMTs) and to manage them properly.

Esophageal GCTs are usually asymptomatic [6]. With the widespread use of routine endoscopy, the incidence of accidental findings of GCTs has increased. Forceps biopsy, endoscopic ultrasonography (EUS) and EUS-guided fine-needle aspiration (EUS-FNA) were used to improve the preoperative diagnosis of GCTs. However, the prediction of them for esophageal GCTs is still not accurate [7, 8].

Nowadays, management of esophageal GCTs includes surgical treatment, follow-up, and endoscopic treatment [1, 6]. But its optimal management still needs further study. In recent years, endoscopic resection (ER) for esophageal GCTs has become increasingly recognized for its advantages of less invasiveness, quicker recovery, fewer complications and cheaper compared to surgical treatment. Various techniques have been used in the treatment of esophageal GCTs, such as endoscopic mucosal resection

(EMR), endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER), and endoscopic full-thickness resection (EFTR) [9–13]. However, studies of esophageal GCTs are still lacking.

Recently, some studies of esophageal GCTs have showed a small series of patients on aspects of ER, and they proved that EMR and ESD appear safe and effective for esophageal GCTs that are limited to the mucosal and submucosal layers [7, 8, 11, 14–16]. However, rare cases involved esophageal GCTs derived from the muscularis propria (MP) layer [6, 7, 12, 15]. And no case was to assess the safety, efficacy and long-term prognosis of endoscopic submucosal excavation (ESE) in esophageal GCTs. Therefore, the aim of our study was to evaluate endoscopic features and ER of esophageal GCTs.

Methods

Patients

This was a retrospective study conducted at a single center, enrolling 22 patients with pathologically diagnosed esophageal GCTs in the First Affiliated Hospital of Zhengzhou University from February 2012 to December 2020. Enhanced computed tomography (CT) of the chest and upper abdomen was performed to assess whether esophageal abnormalities are detected and whether metastases are present before ER. The mucosal surface and mucosal color of the lesions were observed by routine endoscopy. And EUS was performed to identify the maximum diameter, echogenicity and origin of the lesions in all patients. Informed patient consent was obtained before ER and the study was approved by the Ethics Committee at our hospital.

Endoscopic Resection

All ER (EMR, ESD, and ESE) procedures were performed by expert endoscopists using a single-channel endoscope (GIF-Q260J, Olympus) and EUS (MAJ-935, Olympus, UM-3R, Olympus). Other equipment used during the procedure included transparent hood (D-201-11802; Olympus), injection needle (NM-4L-1; Olympus), hook knife (KD-620LR; Olympus), insulated-tip (IT) knife (KD-610L; Olympus), hemostatic forceps (FD-410LR; Olympus), snare (SD-9L-1; Olympus), hemostatic clip (HX-600-135; Olympus) and high-frequency generator (ICC200; ERBE).

For EMR, first, in order to create a large submucosal space, injection was done on the outside of the lesion edge with a mixture of adrenaline and saline to the lesion. Then, electrosurgical snare was used to remove the entire lesion. Sometimes, a transparent cap assists in pulling up the lesion for better complete resection.

For ESD, first, the IT knife was used to make the normal mucosa surrounding the lesion at 0.5 cm from the lesion. Next, for the same purpose as EMR, submucosal injection was performed on the outside of the marking dots. Then, the mucosa was incised along the lateral edge of the marker with the hook knife and

extended to the submucosa with the IT knife. Then the IT knife and transparent cap help to dissect the lesion until en bloc resection is complete. Finally, the forceps removed the lesion.

For ESE, marking and submucosal injection procedure is consistent with ESD. Next, the longitudinal incision was used to incise the mucosa with the hook knife. Then, the IT knife and transparent cap are used to separate the lesion from the submucosal and muscle tissue around the tumor. Submucosal injections are used throughout the process of stripping the tumor outside the capsule. Finally, the forceps removed the lesion.

Histopathological Evaluation

The resected specimens were fixed in formalin solution, and routine hematoxylin and eosin (H&E) staining and additional immunohistochemistry (IHC) were performed and observed under an optical microscope for evaluation and differential diagnosis. Soluble protein-100 (S-100) positive is a necessary condition for the diagnosis of GCT. Other IHC examination such as SRY-related HMG-box 10 (SOX-10), neuron specific enolase (NSE), cluster of differentiation 68 (CD68), CD34, CD117, smooth muscle antibody (SMA), cytokeratin (CK) and desmin, were performed selectively. En bloc resection was defined as the removal of the entire lesion at one time. The R0 resection was defined as a resected lesion with negative horizontal and vertical margins.

Follow-up And Statistical Analysis

Patients were scheduled for follow-up routine endoscopy at 3, 6, and 12 months after resection and thereafter routine endoscopy every 1 year to assess recurrence or metastasis. Continuous variables that obey to a normal distribution were expressed as mean $\pm$ standard deviation (SD) with ranges. If they do not obey to a normal distribution, they were expressed as median with upper quartile and lower quartile (P_{25} , P_{75}). Categorical variables were expressed as frequencies and proportion. All statistical analysis was performed with the SPSS 25.0 software (SPSS Inc., Chicago, IL, USA).

Results

22 patients (12 males and 10 females) with esophageal GCTs were identified. The mean age at the time of diagnosis was 46.4 ± 10.5 years old (range 26–67 years old). 12 patients underwent the CT examination. Only 1 patient (8.3%) was found with esophageal thickening, while the rest (91.7%) showed no abnormalities.

The majority of endoscopic appearance of esophageal GCT were non-specific. For all the cases, the tumor was solitary. Among the 22 lesions, lesions were located in the upper, middle and lower esophagus in three, six and thirteen cases respectively. 21 lesions (95.5%) had a smooth mucosal surface, and 1

lesion (4.5%) had concavity. In addition, 14 lesions (63.6%) exhibited white-to-yellow discoloration, and 8 lesions (36.4%) were normal mucosal color.

EUS was performed in all patients. The maximum diameter of these lesions ranged from 2 to 11.6 mm with a mean size of 5.7 mm. Among the lesions, 10 lesions (45.5%) were confirmed to be located in the mucosa layer, 10 lesions (45.5%) were located in the submucosa layer and 2 lesions (9.0%) were in the MP layer. Among the lesions, 15 lesions (68.2%) showed hypoechoic signal, and 7 lesions (31.8%) showed hyperechoic signal (Table 1).

Table 1
Clinicopathological characteristics and endoscopic
features of the 22 patients with esophageal Granular cell
tumors.

Patients	Values
Lesions, n	22
Gender, female n (%)	10 (45.5)
Age (mean $\pm$ SD, year)	46.4 $\pm$ 10.5
Symptoms, n (%)	
Epigastric discomfort	13 (59.1)
Regurgitation	10 (45.5)
Belching	5 (22.7)
Retrosternal discomfort	2 (9.1)
Asymptomatic	2 (9.1)
Lesion location, n (%)	
Upper	3 (13.6)
Middle	6 (27.3)
Lower	13 (59.1)
Mucosal surface, n (%)	
Smooth	21 (95.5)
Concavity	1 (4.5)
Mucosal color, n (%)	
White-to-yellow	6 (27.3)
Normal	16 (72.7)
Maximum diameter (mean $\pm$ SD, mm)	5.7 $\pm$ 2.2
Echogenicity, n (%)	
Hypoechoic	15 (68.2)
Hyperechoic	7 (31.8)
Layer of origin, n (%)	
Mucosa	10 (45.5)

Patients	Values
Submucosa	10 (45.5)
Muscularis propria	2 (9.0)

EMR(n = 17) and ESD(n = 3) were performed in 20 lesions located in the mucosa or submucosa, and ESD (n = 1) and ESE (n = 1) were performed in 2 lesions located in the MP layer (Table 2). Technical success was achieved and pathological diagnosis was confirmed in all patients. En bloc resection was achieved in 20 lesions (90.9%). The R0 resection was achieved in 20 lesions (90.9%). No patients experienced intraoperative perforation or delayed bleeding in the mean length of postoperative hospital stay of 4.2 ± 2.1 days (range 1–9 days). The mean follow-up time was 48.1 ± 27.2 months (range 2-102 months). At follow-up, 1 patient died of intracerebral hemorrhage 52 months after EMR (case 20), and all patients showed no recurrence or metastasis at follow-up.

Table 2
Clinical outcomes of endoscopic resection for the 22 patients with
esophageal Granular cell tumors.

Patients	Values
Resection methods, n (%)	
EMR	17 (77.3)
ESD	4 (18.2)
ESE	1 (4.5)
En bloc resection, n (%)	20 (90.9)
R0 resection, n (%)	20 (90.9)
Intraoperative perforation, n (%)	0 (0.0)
Delayed bleeding, n (%)	0 (0.0)
Mean length of hospital stay, days (mean ± SD, days)	4.2 ± 2.1
Additional surgery, n (%)	0 (0.0)
Recurrence or metastasis, n (%)	0 (0.0)
Follow-up (mean ± SD, months)	48.1 ± 27.2
EMR endoscopic mucosal resection, ESD endoscopic	
submucosal dissection, ESE Endoscopic submucosal excavation	

Discussion

Esophageal GCTs are the most common GCTs in the gastrointestinal tract, accounting for approximately 2–3% of all GCTs [3]. It can occur at any age, but it is more likely to occur in 40–60 years old [7]. Our study reconfirmed this result. Previous studies showed that the frequency of esophageal GCTs was higher in females than in males, which is not consistent with a female/male ratio of 1:1.2 (10/12) in our study [7]. Most tumors are solitary and located in the middle and lower esophagus [1, 16]. All cases in our study were solitary, and 86.4% (19/22) of lesions were located in the middle and lower esophagus. However, esophageal GCTs can appear as multiple tumors, and multi-organs simultaneously or asynchronously [15, 17].

Various methods have been used to diagnose esophageal GCTs, but preoperative diagnosis is still difficult. In our study, of the 12 patients who underwent CT examination, only 1 patient (8.3%) was found with esophageal thickening, while the rest were normal. The typical endoscopic appearance of esophageal GCTs shows a white-to-yellow, smooth-surfaced lesion with normal overlying mucosa [1, 6, 15, 16, 18]. Similar to previous reports, 14 lesions (63.6%) exhibited a typical yellowish appearance, but this feature may cause the misdiagnosis of lipoma, particularly in hyperechoic lesions on EUS. Besides, although superficial erosion or ulceration of esophageal GCTs is rare, further EUS differentiation between GCTs and gastrointestinal stromal tumors (GISTs) is needed [19].

Recently, EUS has improved the preoperative diagnosis of esophageal GCTs. The typical EUS pattern of esophageal GCTs appears as a hypoechoic, mildly inhomogeneous, and smooth-edged lesions located in mucosa or submucosa [6, 15]. But, 6 cases of esophageal GCTs derived from the MP layer have been reported in previous studies and 2 were reported in our study, suggesting that GCTs do not originate merely in mucosa and submucosa [6, 7, 12, 15]. In addition, hyperechoic lesions have also been gradually reported (7 cases in our study). In previous studies, most leiomyomas also showed hypoechoic images originated from muscularis mucosa or the MP layer. But the brightness of GCTs on EUS was similar to that of the submucosal layer, and it was significantly higher in comparison to leiomyomas, which can largely help in differential diagnosis of esophageal GCTs and leiomyomas [18].

Pathological diagnosis is still the gold standard. Forceps biopsy or EUS-FNA could provide histopathological information, which may help distinguish esophageal SMTs and guide the treatment strategy. However, the accuracy of them for the diagnosis of esophageal GCTs is also low because the specimen obtained was not adequate. In addition, forceps biopsy and EUS-FNA may increase the risk of tumor capsule damage and the difficulty of R0 resection [8]. Therefore, forceps biopsy and EUS-FNA was not performed in the patients in our study.

Adequate tumor specimens are a precondition for a correct pathological diagnosis. Pathologically, the tumor cells are separated by fibers into distinct nests or clusters, consisting of spherical or polygonal large cells with abundant eosinophilic granules cytoplasm and small, round, centrally located nucleus [6, 8]. In addition, schwannomas derived from Schwann cells, present as spindle tumor cells, sometimes with a lymphoid cuff [20]. If pathological characteristics are not enough for the diagnosis, IHC staining will be necessary. According to previous studies, some positive stainings have also been reported, such as S-100,

periodic acid-Schiff (PAS), NSE, SOX-10, CD68, CD56 and nestin [7, 16]. Negative markers, which include CD34, CD117, SMA, CK and desmin, have also been reported [7, 16]. Conversely, esophageal leiomyomas are positive for SMA and desmin, and negative for S-100; GISTs are positive for CD117 and CD34, and negative for S-100 [7, 21].

According to previous studies, approximately 1–2% of esophageal GCTs are malignant [4–6]. Malignant GCTs usually present as tumor cell necrosis, tumor cell spindling, large nucleoli, increased mitotic activity (> 2 per 10 high power fields), increased nuclear size, and nuclear pleomorphism [4]. Meanwhile, Ki-67 positive cells ($> 10\%$) and p53 positive cells ($> 50\%$) were highly associated with malignancy [4]. In addition, remote metastasis after ER is reliable clinical evidence for the diagnosis of malignancy, however it remains unclear whether infiltrative features are credible evidence [6, 22]. None of the 22 patients in our study had postoperative pathology suggestive of malignancy, and there was no recurrence or metastasis during follow-up. This may suggest that esophageal GCTs have a lower malignant potential than other organs, consistent with some series of studies on ER for esophageal GCTs [8, 11, 15].

Management of esophageal GCTs includes surgical treatment, follow-up, and endoscopic treatment. Surgical treatment for esophageal GCTs, including open surgery and thoracoscopic surgery, is the most invasive approach with the high complications. Nowadays, it is only performed when malignancy is suspected or ER is contraindicated [1, 6]. EUS follow-up and ER become the preferred recommendation. For incidental findings, asymptomatic and relatively small (≤ 10 mm) esophageal GCTs, the patient should be involved in the decision to follow up or resect [6, 22]. However, long-term follow-up may increase the financial and psychological burden on the patient and may lead to missed diagnosis of malignancy, so ER is usually more acceptable. For symptomatic or large (> 10 mm), ER should be chosen [6, 22]. In the past, dehydrated alcohol injection, YAG laser ablation and argon plasma coagulation have been used for the endoscopic treatment of GCTs [22, 23]. But they have been rarely used since they cannot provide a complete removal of the lesion and a definitive tissue diagnosis. Currently, various ER techniques have been used in the treatment of esophageal GCTs, such as EMR, ESD, ESE, STER and EFTR. Appropriate approach of ER should be selected according to the origin and size of the lesion.

In previous studies, EMR appears safe and effective for treating esophageal GCT limited in the mucosal and submucosal layers and ≤ 10 mm in size [7, 14–16]. And ESD is also used in the treatment of GCTs located in the mucosal or submucosal layers, especially for those > 10 mm because of its high en bloc resection and R0 resection [8, 11]. These were demonstrated again in our study. However, as esophageal GCTs derived from the MP layer are gradually being reported, ER of them has become an inevitable topic. The literature over the past 20 years reported 6 cases of esophageal GCTs derived from the MP layer, of which 2 were treated surgically, 1 was treated with STER, 1 was treated with EFTR, 1 was followed up, and the treatment approach in 1 case was unclear [6, 7, 12, 13, 15]. STER is inspired by peroral endoscopic myotomy and natural orifice transluminal endoscopic surgery and has been gradually applied for treating esophageal SMTs derived from the MP layer. One systematic review and meta-analysis study proved the long-term efficacy and safety of STER for upper gastrointestinal SMTs, and all of STER-related complications can be managed conservatively [24]. In previous studies, four cases of

STER treated esophageal GCTs were reported, three of which originated in the submucosa and one in the MP layer [6, 12]. No tumor recurrence or metastasis was observed during the long-term follow-up. Besides, EFTR has also been reported for the treatment of esophageal SMTs derived from the MP layer [13, 25]. Although safety and efficacy have not been systematically evaluated, EFTR offers a novel option for the treatment of esophageal GCTs derived from the MP layer. Without doubt, more cases are needed to evaluate the long-term prognosis of STER and EFTR for esophageal GCTs derived from the MP layer.

Of 2 esophageal GCTs derived from the MP layer in our study, 1 lesion underwent ESD, and 1 lesion underwent ESE. ESE is adapted from ESD for the treatment of upper gastrointestinal SMTs derived from the MP layer [26]. The ESE longitudinally incises the mucosa and bluntly separates the complete tumor, which makes the ESE procedure simple and quick. ESE has been applied to the esophageal, cardiac and gastric lesions, but the risk of bleeding and perforation is higher in the esophagus compared to other locations, due to the narrow lumen and thin wall without a serosal layer. As techniques for handling perforations advances, perforation is no longer an obstacle to performing ESE, and meanwhile, ESE will mature to allow fewer perforations. One retrospective study found that both STER and ESE were safe and effective techniques for the treatment of esophageal SMTs derived from the MP layer and have similar overall complications [27]. Besides, ESE is easier to operate than STER and 95% of esophageal GCTs are less than 20 mm in size [16]. So ESE has great potential in treating esophageal GCTs. In our study, one patient who underwent ESE had no intraoperative perforation or delayed bleeding during hospitalization and no metastasis or recurrence during 84-months follow-up. This is the first report to assess the safety, efficacy and long-term prognosis of ESE in esophageal GCTs.

There were some limitations in our study. First, this was a retrospective single-center study with a limited number of patients included. Second, we identified patients from the pathology database, which may have a selection bias. The patients we finally identified did not include patients who had surgery treatment or follow-up, so we did not compare clinical outcomes of surgery treatment or follow-up with ER.

In conclusion, esophageal GCTs are rare, and typical endoscopic features can improve the preoperative diagnosis of esophageal GCTs. Histopathology and IHC are necessary for diagnosis and distinguish between benign and malignant. ER is safe and effective for management of esophageal GCTs. Clinically, the appropriate approach of ER should be selected according to the origin and size of the lesion.

Abbreviations

GCTs

Granular cell tumors; EUS:endoscopic ultrasonography; EUS-FNA:EUS-guided fine-needle aspiration; SMTs:submucosal tumors; ER:endoscopic resection; EMR:endoscopic mucosal resection; ESD:endoscopic submucosal dissection; STER:submucosal tunneling endoscopic resection; EFTR:endoscopic full-thickness resection; MP:muscularis propria; ESE:endoscopic submucosal excavation.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of ZhengZhou University. Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Consent for publication

Not applicable.

Availability of data and materials

No additional data are available.

Competing interests

All authors have no Competing interests to disclose.

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Authors' contributions

KL and YZ designed the study and drafted the manuscript. BL and DL provided technical support. QZ, HY and KL were responsible for the analysis and interpretation of data. BL and KL were responsible for the critical revision. All authors read and approved the final manuscript.

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