Clinical characteristics and surgical treatment of oesophageal gastrointestinal stromal tumours

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Abstract

Objective: Oesophageal gastrointestinal stromal tumours (GISTs) are extremely rare. The preoperative diagnosis is complicated by lack of specificity and the clinical features of patients with oesophageal GISTs need to be fully studied. Methods: We have reviewed retrospectively the medical records of those patients who are treated surgically for oesophageal GISTs in our two hospitals. Results: Eight oesophageal GISTs were identified among the 63 oesophageal mesenchymal tumours in our two hospitals in the past 30 years. Of the eight patients, the male:female ratio was 5:3; the median age of the patients was 57 years (range 49—71 years). Dysphagia was the most common symptom, and all cases were diagnosed postoperatively. The tumours were resected by enucleation or oesophagectomy. The median follow-up was 59 months, ranging from 14 to 202 months, with four of the patients succumbing to the disease, among them two with recurrence and another two with metastasis. Conclusions: Our study indicates that oesophageal GIST is rather rare, and it has relatively high recurrence and mortality rates, especially for patients with large tumours (larger than 9 cm). At present, surgical resection and postoperative diagnosis remain the mainstay for treatment of patients with oesophageal GISTs in China.

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Keywords: Oesophageal GISTs; Clinical characteristics; Surgical treatment; Prognosis

1. Introduction

Gastrointestinal stromal tumours (GISTs), the most common mesenchymal neoplasm of the gastrointestinal (GI) tract, occur most commonly in the stomach and very rarely in the oesophagus. Mazur and Clark first used the term ‘GIST’ in 1983 [1]. The only analysis of multiple patients with oesophageal GISTs has been a report on 17 cases by Miettinen et al. [2] and another report on 18 cases by Abraham et al. [3]. Most descriptions of surgical cases have been limited to single-patient case reports [4—9]. For a better understanding of this rare disease, we reviewed the clinical data on eight cases of oesophageal GISTs at the First and Second Hospitals of Lanzhou University in China from 1978 to 2008.

2. Materials and methods

All oesophageal GISTs, which were diagnosed during the 30-year course from 1978 to 2008 at the First and Second Hospitals of Lanzhou University in China, were retrospectively analysed. A computerised and a manual search of the medical records database for ‘mesenchymal tumours of the oesophagus’ was performed and 63 cases were found. Tissue samples collected from each patient were probed with the following antibodies: CD-117 (c-kit; monoclonal antibody, diluted at 1:100; Dako, Carpinteria, CA, USA), CD-34 (monoclonal antibody at 1:150; Dako), a-smooth muscle actin (SMA; monoclonal antibody at 1:150; Dako), S-100 (polyclonal antibody at 1:300; Dako) and Ki-67 (Dako).

Management guidelines for oesophageal GISTs have been defined by uniform consensus of the National Comprehensive Cancer Network (NCCN) [10] and the European Society of Medical Oncology (ESMO) [11]. Data, including clinical features, radiographs and pathologic slides, were collected and re-analysed by two pathologists. The disclosures of the
3. Results

Eight oesophageal GISTs were identified among these 63 oesophageal mesenchymal tumours and their medical records were complete; the frequency of occurrence of the tumours is 12.7% (95% confidence interval (CI): 4.5—20.9%). The diagnoses of the eight patients were confirmed after histopathological and immunohistochemical analyses of tissue specimens by two pathologists. The clinical features of these eight cases are summarised in Table 1. There were five men (62.5%) and three women (37.5%) ranging in age from 49 to 71 years (median age, 57 years). The most common complaint was dysphagia, which occurred in five patients (5/8); one patient had epigastric pain and GI bleeding; another patient had dysphagia and also presented with GI bleeding; only two patients (2/8) had no symptoms; weight loss was documented in four patients, and none had a family history of malignancies. Intervals between the onset of symptom occurrence and the time of diagnosis ranged from 1 to 120 months and the median interval was 4 months.

All patients underwent oesophagoscopy examinations (Fig. 1(A)) and a barium swallow check-up (Fig. 1(B)). Two of these patients underwent oesophagoscopy and endoscopic ultrasound (EUS) examinations that demonstrated smooth, submucosal lesions. All tumours for which the level of location was documented occurred in the lower third of the oesophagus and five tumours also involved the gastro-oesophageal junction. All patients underwent surgical resection, although none of the cases in our study had a preoperative histological diagnosis. Five patients with the tumour size larger than 9 cm underwent a partial resection of the oesophagus under a thoracotomy, and then underwent an oesophagogastrostomy. The other three patients with the tumour size smaller than 7.5 cm underwent tumour excision involving surrounding muscularis without mucosa under a thoracotomy. All tumours were completely resected with margins that were microscopically clear (R0); and none of the patients received radiation, chemotherapy or imatinib therapy perioperatively.

Tumour lengths ranged from 3 to 16 cm with a median length of 9.25 cm. The largest four tumours (patients 1, 2, 4 and 6) were larger than 9 cm and bulged into the posterior mediastinum, appearing radiologically as mediastinal masses (Fig. 1(C) and (D)). The smallest tumour (patient 3) was purely intramural and the other three patients had tumours with growth patterns that were intramural and intraluminal. All of the tumours adhered to the mucosa or the muscularis.

Tissues from all tumours were analysed using histopathological and immunohistochemical techniques. The histopathological and immunohistochemical features of these eight cases are summarised in Table 2. In five tumours, the clinical data for the patients were approved by the Institutional Review Board of the First and Second Hospitals of Lanzhou University. Follow-up information was obtained by mail, telephone and personal interviews. Data were collected up to 31 October 2008. Complete follow-up information, including survival status and causes of death, the clinical features, treatment procedures and outcomes of the eight patients, was obtained and analysed.
cut surface showed foci of necrosis. Seven cases (87.5%) were of spindle-cell type (Fig. 2(A)) and one case (12.5%) was of epithelioid cell type; none showed evidence of mixed cell types. Mitotic indices varied from 0 to 30 mitoses per 50 high-power fields (HPFs) and four tumours had mitotic indices >5 mitoses per 50 HPF. All tumours were positive for CD34 (Fig. 2(B)) and CD117 (Fig. 2(C) and (D)). Only one patient (12.5%) was positive for α-SMA and none was positive for S-100. Lymph nodes were resected in six of the eight patients, and no lymph nodes metastasis was found.

All eight patients underwent successful resection and no short-term complications occurred postoperatively. Follow-up data were obtained from all patients. The follow-up period ranged from 14 to 202 months and the median period was 59 months. Four patients recurred, and two of them were verified to have hepatic metastasis. All of the four patients died of their GISTs with a disease-specific death rate of 50% (four of eight patients). These patients all had tumours larger than 9 cm and mitotic index >5 mitoses per 50 HPF.

4. Discussion

GISTs are the most common subset of mesenchymal tumours of the GI tract and account for up to 3% of GI-tract malignant tumours. These tumours most commonly arise from the stomach (60—70%), followed by the small bowel (25—35%), and are rare in the colon and oesophagus[12,13]. In the oesophagus, squamous carcinoma and adenocarcinoma are the most common malignant tumours, and leiomyomas are the most frequent mesenchymal neoplasm. GISTs have been documented very rarely in the oesophagus[14]. Although the relative frequency of oesophageal GISTs among all oesophageal mesenchymal tumours has been reported to be approximately 25%[2], in our survey, only eight oesophageal GISTs were identified among 63 oesophageal mesenchymal tumours (12.7%). Thus, our data indicate that oesophageal GISTs are rare. In this retrospective study, we report the so-far largest surgical series of oesophageal GISTs.

It is currently thought that GISTs originate from a precursor cell pool with differentiation towards the Cajal cell phenotype[15—17]. Interstitial cells of Cajal (ICC) derive from myeloid stem cells and are pacemaker cells that are involved in the regulation of motility of cells of the GI tract. GISTs exhibit typical activating mutations of KIT or platelet-derived growth factor receptor alpha polypeptide (PDGFRA) proto-oncogenes, which are the likely causal molecular events[18,19].

We describe the clinical features of oesophageal GISTs resected during the past 30 years in two hospitals. Oesophageal GISTs occurred most frequently in middle-aged males. The presenting signs and symptoms depended on the

<table>
<thead>
<tr>
<th>Case</th>
<th>Cellular pattern</th>
<th>Mitosis/50HPF</th>
<th>Necrosis</th>
<th>CD117 (c-kit)</th>
<th>CD34</th>
<th>SMA</th>
<th>S-100</th>
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<td>0</td>
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<td>+</td>
<td>Focal</td>
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<tr>
<td>4</td>
<td>Epithelioid</td>
<td>16</td>
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<td>+</td>
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</tr>
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<td>–</td>
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<tr>
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<td>–</td>
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size and location of the tumour. The most common complaint was dysphagia, and the tumour mostly occurred in the lower third of the oesophagus. In general, a preoperative diagnosis of GISTs is difficult. The reasons for the difficulty of diagnosis may be associated with the lack of specificity of the symptoms and the similar endoscopic and radiographic appearance with the far more common oesophageal leiomyoma.

Whether oesophageal masses should be biopsied preoperatively is still a controversial issue. Some authors [20–22] have suggested that EUS-guided fine-needle aspiration (FNA) may be used to differentiate oesophageal GISTs from leiomyoma. However, NCCN guidelines do not suggest preoperative biopsy of a resectable mass, for GISTs may be soft and fragile, and biopsy may cause haemorrhage and increase the risk of tumour dissemination. In fact, many pathologists cannot guarantee a definitive diagnosis using such a small tissue obtained by FNA. In addition, a core-needle biopsy may be inconclusive if a necrotic or haemorrhagic portion of the tumour is aspirated [10]. Furthermore, the biopsy may increase the risk of oesophageal leak after a submucosal resection. Thus, postoperative immunohistochemical assessment is reliable in the diagnosis of any suspected GIST. CD-117, CD-34, SMA and S-100 are the antibodies used most frequently; about 95% of GISTs are positive for KIT (CD117), 60–70% for CD34, 30–40% for SMA and 5% for S-100 protein [10,11].

With a preoperative diagnosis, what is the ideal resection? Surgery has been the mainstay of therapy for oesophageal GISTs. A complete resection of tumour that does not have evidence of metastasis should be the initial therapy if the tumour is technically resectable with acceptable risk of morbidity [10,11]. Oesophageal GISTs resections are essentially limited to either simple enucleation or oesophagectomy. However, which surgical procedure should be performed remains controversial with regard to tumour size. A recent report [21] suggests that oesophagectomy is the preferred method for larger tumours. None of the patients in our study had recurrence or metastasis if the tumours were excised along with the surrounding muscle keeping the mucosa intact; however, the prerequisite was that the size of the tumour be less than 7.5 cm. Therefore, the successful enucleation for oesophageal GISTs should be complete gross resection with an intact pseudo-capsule and negative microscopic margins. Bearing in mind the limited cases and follow-up period, it still needs to be proved by studies with large sets of cases. In addition, there was no lymphatic spread of GISTs in the study; therefore, the lesser nodal dissection was required when resecting compared with other tumours of the oesophagus. Preoperative identification of tumour site is more important than tumour size for deciding the optimal surgical strategy and the location of the tumour is also a very important prognostic factor to oesophageal GIST. Large tumours located close to the gastro-oesophageal junction are rare and may be difficult to resect with adequate margins [23]. In the study, we found that five of the eight patients involved the gastro-oesophageal junction, and four of the five (80%) recurred and succumbed to the disease. Hence, it could be concluded that the tumour site of oesophageal GIST, especially those involved distally, is a high-risk indication for grave prognosis.

The predominant cause of death in our cases was the malignant behaviour of oesophageal GISTs. Oesophageal GISTs are unique in their malignant potential and there is still no accepted staging system. In the NCCN guidelines defining risk of aggressive behaviour, GISTs are classified into none-, very low-, low-, moderate- and high-risk groups, depending on the size and mitotic index of the tumour. Gastric GISTs are diagnosed as high risk when the following criteria are met: tumour size >5 cm and mitotic index >5/50 HPF. Our analysis showed that three of the four patients, all of whom had tumours larger than 9 cm and a mitotic index >5 mitoses per 50 HPF, died of the disease after surviving postoperatively for approximately 5 years. Based on this, we suggest that oesophageal GISTs that are larger than 9 cm should be regarded as malignant and be treated with an oesophagectomy or even en bloc resection if contiguous organs are involved. This should be followed by postoperative adjuvant therapy such as imatinib. A prerequisite for neo-adjuvant or induction imatinib mesylate therapy for GIST is a preoperative diagnosis. Unfortunately, the eight patients involved in this study were not diagnosed as oesophageal GISTs, either preoperatively or postoperatively; hence, no tyrosine kinase inhibitors (TKIs) were applied, although TKIs may allow a higher R0 resection rate. For oesophageal GISTs smaller than 9 cm, an oesophagectomy should also be performed if the tumour exhibits malignant behaviour such as mucosal destruction or ulceration before or even during surgery.

In conclusion, oesophageal GISTs are extremely rare but have relatively high recurrence and mortality rates. These tumours occur most commonly in middle-aged males, and usually locate at the lower third of the oesophagus. The symptoms are similar to oesophageal carcinoma but the endoscopic and radiographic appearances are similar to oesophageal leiomyoma. The liver is the most common organ for metastasis. To obtain accurate diagnosis, prompt immunohistochemical staining with CD-117, CD-34, SMA and S-100 should be carried out on all suspicious polypoid masses of the oesophagus. The successful enucleation for oesophageal GISTs should be complete gross resection with an intact pseudo-capsule and negative microscopic margins; for those patients with tumours larger than 9 cm, a mitotic index >5 mitoses per 50 HPF and showing no evidence of metastasis, extensive resection and oesophagectomy should be the initial therapy.

Acknowledgement

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References


