Laparoscopic resection for a large gastrointestinal stromal tumor (GIST) with diaphragm invasion following preoperative imatinib treatment: A case report

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A B S T R A C T

INTRODUCTION: Neoadjuvant imatinib for large GISTs may prevent tumor rupture and the need for extended surgery by reducing tumor size. In this study, we present a case of large gastric GIST with diaphragm invasion, due to the patient receiving laparoscopic resection following preoperative imatinib treatment.

PRESENTATION OF CASE: A 72-year-old woman was hospitalized with left hypochondriac pain for a month. Examinations revealed a large heterogeneous gastric mass measuring 80 mm in size, arising from the greater curvature of the corpus. The mass invaded the left thoracic diaphragm. Treatment with imatinib at an initial dosage of 400 mg/day was initiated. After a further two months of follow-up, the lesion had sustained reduction to 50 mm in size, however, the invasion to the diaphragm remained. The patient eventually underwent laparoscopic partial gastrectomy and partial resection of the diaphragm with curative intent. Adjuvant chemotherapy was initiated at one month after the surgery, however, was discontinued due to nausea. After one-year follow-up, no recurrence was noted.

DISCUSSION: Neoadjuvant imatinib may shrink tumor size remarkably and prevent tumor rupture during surgery, and thus lead to increased rates of complete resection. To date, several publications have directly compared the oncologic results between laparoscopic and open resection for GISTs. In the present case, the tumor was movable, and moderately fixed on diaphragm. It was favorable condition for laparoscopic surgery.

CONCLUSIONS: This is the first report of a large gastric GIST invading the diaphragm that was successfully treated by laparoscopic resection after tumor reduction by neoadjuvant imatinib.

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1. Introduction

Gastric submucosa tumor (SMT) is found in 0.3% of middle-aged adults by health examination, half of which are considered to be neoplastic [1]. Typical SMTs are gastrointestinal stromal cell tumors (GISTs), leiomyomas, and schwannomas, and the most common is GIST (80%) [2]. Surgical resection is the only curative treatment for GIST. Independent prognostic factors for recurrence after resection include tumor size, mitotic count, tumor location, and tumor rupture. GISTS with high-risk features such as large tumor size, high mitotic count, or tumor rupture have poor prognosis after resection; more than half of the patients with such tumors suffer from recurrence within 5 years after surgery. For such high-risk cases, adjuvant treatment has been attempted to reduce recurrence rate. Adjuvant imatinib prolonged recurrence-free survival, but eventually many patients showed recurrence after termination of adjuvant imatinib [3–5]. Neoadjuvant imatinib may prevent tumor rupture and the need for extended surgery by reducing the tumor size by approximately 35%, especially for large GISTS, as shown in a previous phase II study [6]. Laparoscopic gastric surgery...
has gained popularity in surgical oncology since it embraces benefits such as reduced postoperative morbidity and shorter length of hospital stay [7]. In the present study we present a case of large gastric GIST with diaphragm invasion, due to a patient receiving laparoscopic resection following preoperative imatinib treatment. This case report has been prepared in line with the SCARE criteria [8].

2. Case presentation

A 72-year-old woman was hospitalized with left hypochondriac pain for a month. All biochemical studies were normal. Abdominal CT scan revealed a large heterogeneous gastric mass with contrast effect measuring 80 mm in size, arising from the greater curvature of the corpus. The mass invaded the left thoracic diaphragm and left hepatic lobe (Fig. 1a, b). Upper gastrointestinal endoscopy (UGI) detected well-circumscribed submucosal tumor at the greater curvature of the gastric body (Fig. 1c). Although a biopsy didn’t confirm the diagnosis of GIST, CT imaging and UGI showed the classical features of GIST. In 18F-fluorodeoxyglucose position emission tomography (18F-FDG PET)/CT, obviously increased FDG uptake was shown in the tumor (SUVmax, 22.9). There was no evidence of distant metastases on 18F-FDG PET (Fig. 1d). The patient had the potential to receive proximal gastrectomy or total gastrectomy with the resection of the diaphragm for radical treatment. We initiated preoperative adjuvant chemotherapy with imatinib to achieve a reduction of operative risks and functional preservation. Treatment with imatinib at an initial dosage of 400 mg/day was initiated. At two months after the initiation, the CT scan showed that the primary tumor had reduced to 50 mm on its largest axis. Poor tolerance to treatment (ie, nausea, vomiting, and rash on the skin) required a reduction in the dosage to 300 mg/day. One week afterwards, imatinib treatment was stopped. After further two months of follow-up, CT showed that the lesion had shrunk with a lower contrast effect, however, the invasion to the diaphragm remained (Fig. 2a, b). UGI also revealed the tumor shrinkage (Fig. 2c). The patient eventually underwent laparoscopic partial gastrectomy and partial resection of the diaphragm with curative intent. Surgical findings showed that a pedunculated tumor on the fundus wall invading the diaphragm had just appeared after dividing the short gastric and left gastroepiploic vessels (Fig. 3a). We performed gastric division first by linear stapler (Powered Echelon flex, 60-mm cartridges, Ethicon Endo Surgery) with a safety margin, then raised up the tumor by gripping the margin of the stomach wall. Owing to the easy-handling of the tumor, we next resected the diaphragm with a distant margin using an ultrasonic coagulation-cutting device (HARMONIC HD 1000i; Ethicon Endo Surgery) (Fig. 3b, c). The defect was closed by running suture using the V-Loc polybutester (PBT) nonabsorbable wound closure device (Covidien, Mansfield, MA) (Fig. 3d, e). Operative time was 146 min. Estimated blood loss was 20 mL. The resected tumor was approximately 50 × 40 × 35 mm in diameter (Fig. 4a). Micro-scopical assessment showed the presence of stromal spindle cells invading the diaphragm (black dots line) and excision was completed. Tumor cells were replaced by hyalinized collagen and viable cells were sparse (Fig. 4b, c). Less than 5 mitoses / 5 mm² were seen. Immunohistochemical analysis showed c-kit (+), CD34 (+), Ki-67 index of 3.25% (Fig. 4d). From these findings, the tumor was diagnosed as a low-risk GIST by the Fletcher classification.

Post-operative recovery was uneventful. Adjuvant chemotherapy (imatinib, 300 mg/day) was initiated at one month after the surgery, but she was discontinued due to nausea. After one-year follow-up, no recurrence was noted.

3. Discussion

In this case, the large gastric GIST with diaphragm invasion was resected completely by laparoscopy after neoadjuvant imatinib treatment. There is no previous report of laparoscopic resection for large GIST with diaphragm invasion.

This patient received neoadjuvant chemotherapy without a pathological diagnosis. CT scan is the most widely used imaging tool for detecting GIST because it allows an accurate evaluation of tumor size and the anatomical relationship with adjacent organs, but the definitive diagnosis of GIST is obtained with histological

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![Fig. 1. a. Axial image of abdominal CT scan showed a large heterogeneous gastric mass with contrast effect measuring 80 mm in size, arising from the greater curvature of the corpus. b. Coronal image of CT revealed that the mass invaded the left thoracic diaphragm and left hepatic lobe. c. Upper gastrointestinal endoscopy (UGI) detected a well-circumscribed submucosal tumor in the greater curvature. d. 18F-FDG PET/CT revealed intense 18F-FDG accumulation (SUVmax 22.9) in the tumor and no evidence of distant metastasis.](image-url)
analysis [8,9]. In our case, UGI showed high-risk features indicating malignant potential from the several large protuberating lesions with an irregular border. CT revealed a large tumor with direct invasion to diaphragm, and 18F-FDG PET showed a high-accuracy lesion. We made a mature decision of circumstance diagnosis as GIST. However, for greater certainty, Endoscopic Ultrasound (EUS) and Endoscopic Ultrasound-Fine Needle Aspiration (EUS-FNA) can be done to diagnose this SMT.

Neoadjuvant imatinib treatment may shrink tumor size remarkably and prevent tumor rupture during surgery, and thus lead to increased rates of complete resection. Prospective and retrospective studies have shown that neoadjuvant imatinib therapy effectively decreases tumor size, thereby facilitating the ease of surgery and resulting in organ-preserving operations with less morbidity [10,11]. The median shrinkage rate, in a phase II study by Kurokawa Y. et al., was 35.4%, and no patients showed growth of primary tumors while receiving neoadjuvant treatment [6]. National Comprehensive Cancer Network (NCCN) guidelines state that neoadjuvant chemotherapy is considered if surgical morbidity can be reduced by downstaging the tumor [12]. The duration of neoadjuvant imatinib administration is important to obtain a sufficient response. In a recent study, Tielen et al. reported a median decrease in tumor size by 50% in 57 patients with locally advanced GISTs who underwent surgery after neoadjuvant imatinib treatment (median duration: 32 weeks; range: 1–55 months) [13]. A Japanese phase II study for patients with unresectable or metastatic GIST also revealed that the cumulative response rate reached a plateau after 200 days (Nishida et al., 2008). The timing of this plateau response varies between 4 and 12 months [6,14]. In our case, the patient received neoadjuvant imatinib treatment (400 mg/day) for two months. The original plan was for six months, but it was discontinued due to side effects (nausea and vomiting). There were no Grade 3–4 nausea in a phase-II study, whereas Grade 1–2 of that study occurred in 30% [6]. Side effects include fluid retention, edema, fatigue, and liver profile abnormalities, commonly reversible after drug cessation. Imatinib's toxicity, in general, has

Fig. 2. a. After imatinib mediation, CT revealed an extremely shrunken tumor with a lower contrast effect, while diaphragm invasion still remained. b. UGI also showed the tumor shrinkage.

Fig. 3. a. During the operation, a pedunculated tumor (black arrows) on the fundus wall, invading to diaphragm had just appeared after dividing the short gastric and left gastroepiploic vessels. b, c. After gastric division, resection of diaphragm with the distant margin was performed using an ultrasonic coagulation-cutting device (HARMONIC HD 1000i; Ethicon Endo-Surgery). d, e. Closing defect by running suture using the V-Loc polybutester (PBT) nonabsorbable wound closure device.
been associated with higher dose exposure and long-term usage [15]. Surgical resection with negative margins without lymphadenectomy has been the treatment of choice of gastric GISTs up to now [16]. Wedge resection has been advocated by many investigators for the majority of gastric GISTs [17]. The length of hospitalization was statistically shorter in laparoscopic surgery than in open surgery. Moreover, the operation time was shorter in laparoscopic surgery, although there was no statistical difference [18]. The laparoscopic group was associated with an earlier return of bowel function, earlier resumption of diet and shorter hospitalization [19]. To date, several publications have directly compared the oncologic results between laparoscopic and open resection for GISTs. The long-term disease-free survival for laparoscopic resection, in treating gastric GISTs for tumors > 5 cm size, shows acceptable oncologic results in comparison to historical open resections [20]. Jun-Lin Chi reported that no significant difference in recurrence and death between the laparoscopic and the open groups. In detail, in the laparoscopic group, six patients (9.52%) had recurrence or metastasis and four (6.35%) died due to GISTs; in the open group, 10 patients (15.87%) had recurrence or metastasis and five (7.94%) died due to GISTs [19]. The Japanese clinical practice guidelines for GIST suggest that laparoscopic resection of gastric GISTs smaller than 5 cm appears safe when performed by a skillful surgeon who is thoroughly familiar with the neoplastic characteristics of gastric GISTs [21]. Ronellenfitsch et al. stated that the tumor size did not determine the feasibility of laparoscopic wedge resection, and the location of the gastric GISTs did not directly affect the indication for laparoscopic wedge resection [22]. Whereas Yang et al. reported on the performance of laparoscopic wedge resection for tumors less than 6 cm in diameter [22,24]. The conversion rates reported ranged from 0 to 25%, which was determined to a great degree by the surgeons’ experience and tumor location and not by the tumor size [25]. The most important point is how to handle the large tumor during laparoscopic surgery. In the present case, the tumor was an extra-gastric type meaning it was movable, furthermore it was moderately fixed on the other side. These were favorable conditions for laparoscopic surgery.

After resection of the diaphragm, the defect was closed using a barbed suture. A barbed suture has been adopted across all surgical specialties. We previously reported a case of laparoscopic diaphragm closure using a barbed suture for traumatic injury [26]. The barbed suture closure system can be used for rapid and effective primary defect closure in laparoscopic surgery. The patient has remained alive without recurrence for one year after the surgery. This is the first report of a large gastric GIST invading the diaphragm that was successfully treated by laparoscopic resection after tumor reduction by neoadjuvant imatinib.

4. Conclusions

We certified it was possible to perform laparoscopic resection for large gastric GIST even if it was invading to diaphragm.

Declaration of Competing Interest

The authors report no declarations of interest.

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None of the authors has anything to disclose.
Ethical approval

All procedures used in this research were approved by the Ethical Committee of National Hospital Organization, Kure Medical Center, Chugoku Cancer Center.

Consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent form is available for review by the Editor-in-Chief of this journal.

Authors contribution

Hirofumi Tazawa is the corresponding author and carried out revision of the manuscript. Takahisa Suzuki performed the surgery. Toshiaki Komo participated in the surgery. Shoko Yoshioka participated in the clinical treatments. Kazuya Kuraoka and Akihisa Saito performed the pathological analysis. Hirotaka Tashiro and Shoko Yoshioka supervised the writing of the manuscript. All authors read and approved the final manuscript.

Registration of research studies

Not Applicable.

Guarantor

Hirofumi Tazawa has accepted full responsibility for this work and the decision to publish it.

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