Title. Laparoscopic sphincter-preserving surgery (intersphincteric resection) after neoadjuvant imatinib treatment for gastrointestinal stromal tumor (GIST) of the rectum

Short Running head: Sphincter-preserving surgery for rectal GIST

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Abstract

Background: Gastrointestinal stromal tumors (GISTs) of rectum are rarely found, and radical surgery such as abdominoperineal resection would be necessary for large rectal GIST. On the other hand, therapy for GIST has changed significantly with the use of imatinib. Neoadjuvant imatinib therapy may reduce tumor size and potentially prevent extended surgery. Moreover, when sphincter-preserving surgery is carried out laparoscopically, it can be performed as minimally invasive surgery with preservation of the anus.

Methods: From 2008 to 2011, 5 patients with rectal GIST were treated in our hospital. All patients received preoperative imatinib treatment (400mg/day), and underwent laparoscopic sphincter-preserving surgery after 4-12 months of this treatment.

Results: Initial median tumor size was 31 mm (range, 24- 88). At the time of operation, the median tumor size was 24 mm (range, 11 - 52). Sphincter-preserving surgery was performed in all patients. Three patients underwent laparoscopic intersphincteric resection (ISR), and 2 patients underwent transanal full-thickness local resection and recto-anal anastomosis following laparoscopic ISR. Macroscopically complete resection was achieved, and microscopically the resection margin was not involved of residual tumors. The median duration of postoperative hospital stay was 16 days (range, 13-30). No recurrence occurred in all patients during one to four years.

Conclusions: The present study suggests that neoadjuvant imatinib therapy might be effective to prevent extended surgery for rectal GIST, and laparoscopic sphincter-preserving surgery is a safe and technically feasible. We recommend combination of neoadjuvant imatinib therapy and laparoscopic ISR for locally advanced rectal GIST.

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal malignancy found in the GI tract. GISTs most often arise in the stomach, but may also be found in the rectum (approximately 5 %) [1]. Surgery is the first choice treatment for a resectable GIST, and complete surgical resection is the most effective treatment to reduce the rate of recurrence and to improve the outcome [2]. Radical surgery such as abdominoperineal resection (APR) or more extended surgery which necessitate the removal of adjacent organs would be necessary for locally advanced rectal GIST located very close to the anus.

Imatinib, a small molecule inhibitor of the oncoprotein KIT and PDGFRA, has become the standard treatment for recurrent or metastatic GISTs. [3,4] There are few reports of preoperative imatinib treatment for unresectable or locally advanced primary GISTs [5,6]. Only few reports have described using Imatinib as a neoadjuvant treatment for rectal GIST [7,8]. Imatinib treatment leads to reduced tumor size, improving the chances of complete surgical resection and the preservation of function.

On the other hand, extended indication for laparoscopic surgery is recent breakthrough in the field of rectal cancer surgery. Our previous report also showed that laparoscopic surgery for rectal cancer is technically feasible [9], and laparoscopic intersphincteric resection (ISR) for very low rectal cancer is technically feasible and a safe alternative to laparotomy with favorable short-term postoperative outcomes [10].

We now report 5 patients who were treated by combination of neoadjuvant imatinib therapy and laparoscopic sphincter-preserving surgery (ISR or modified ISR) for large rectal GIST.

Patients and Methods

From 2008 to 2011, 5 patients with rectal GIST were treated in our hospital. Colonoscopy (CS), endorectal ultrasonography (EUS), computed tomography (CT) and magnetic resonance imaging (MRI) were performed in all patients. CS and EUS were used to evaluate tumor size and distance to anal verge. A biopsy of the tumor showed spindle cells with immunoperoxidase stains positive for c-kit, leading to the histological diagnosis of a GIST. CT and MRI were used to evaluate tumor size, tumor invasion, and lymph-node metastasis. All tumors were initially considered to be too large or difficult to remove including resection margin was negative when the surgery of preserving function were performed. All patients declined a recommendation to receive an APR or extend surgery due to complete surgical resection.

We expect neoadjuvant imatinib therapy may reduce tumor size and potentially prevent extended surgery, and then all patients received preoperative imatinib treatment (400mg/day). CS and CT (or MRI) were used repeatedly every 3-6 months to measure tumor response to imatinib treatment. The indication to discontinue preoperative treatment was lack of reduce in tumor size measured clinically. The resectability was determined by CT or MRI. All patients underwent laparoscopic sphincter-preserving surgery after neoadjuvant imatinib therapy.

After surgery, patients were followed up included regular visits every 3months. Clinical examination and CT were obtained every 6 months, and CS was received every 12 months. Postoperative imatinib was given in selected patients for 2 or 3 years. Local and distant recurrences were defined by radiographic and histological findings.

Results

The patient and tumor characteristics are presented in Table 1. The median age was 58 years (range, 33-76), and 4 were male and one was female. Initial median tumor

size was 31 mm (range, 24- 88). The distance from anal verge to the lower margin of the tumor was 3 cm (range, 2- 5). At the time of operation, the median tumor size was 24 mm (range, 11 - 52). Side effect of edema occurred in 3 patients, who recovered with conservative therapy by reduce the quantity of imatinib. The suspicious tumor invasion to adjacent organs (such as the prostate or the vagina or the levator ani muscle) has improved to clear margin by CT or MRI. MRI of the pelvis revealed reduction in tumor size (Figure 1 and 2). We were enabled to complete surgical resection including the possibility of obtaining more safety margin.

All patients underwent laparoscopic sphincter-preserving surgery after 4-12 months of neoadjuvant imatinib therapy. Three patients underwent laparoscopic intersphincteric resection (ISR), and 2 patients underwent laparoscopic modified ISR. ISR was partial ISR but not total ISR. Modified ISR starts with mobilizing rectum with preserving superior rectal artery. Next, transanal intersphinteric dissection and extraction of the recum through the anus is performed. Finally, full-thickness local resection under the direct vision and reconstruction by recto-anal anastomosis is performed. A diverting ileostomy was created in all cases. The median operation time was 269 min (range, 155-352), and the median estimated blood loss was 115 ml (range, 30-340). We did not have any intraoperative complications. Macroscopically complete resection was achieved in all patients. There was no mortality. Postoperative complication occurred in one patient (ileus), but recovered with conservative therapy. The median duration of postoperative hospital stay was 16 days (range, 13-30). Microscopically the resection margin was not involved by residual tumors. One patient was complete response. An ileostomy was closed in all patients after 3-5 months.

The median follow up period was 36 (range, 13-51) months. No recurrence occurred in all patients during one to four years. Postoperative imatinib was given in 3

patients, one patient was treated after a year of surgery and other two patients were still treated continuously at the time of present. The satisfaction of patients was good because preservation of quality of life by avoiding a permanent stoma. The bowel function was kept well, the daily stool frequency was 4-5 times, and the fecal incontinence did not arise. Bladder function was satisfactory because urinary retention or urinary disturbance occurred in no patient. Sexual function was not evaluated due to lack of research.

Discussion

The complete surgical resection is the most effective treatment for GIST to reduce the rate of recurrence and to improve the outcome. Until more effective adjuvant therapy becomes available, the treatment of GISTs will remain primarily surgical; because recurrence occurred in 40% of patients who underwent complete resection, and the disease-specific survival rate was 54% at 5 years [2]. Imatinib has been demonstrated to be a very active agent for tumor control in GIST [11]. Clinical trials have shown that about 50% of patients with a metastatic GIST will have a partial response to imatinib and about 80% will at least have stable disease, and thus imatinib is now considered as the first-line treatment for metastatic GIST [3,4]. In unresectable or locally advanced primary GISTs, preoperative imatinib is a useful tool both to improve resectability and reduce surgical morbidity because patients had tumor shrinkage with a median tumor size reduction of 34% after imatinib treatment [5]. A formal indication to imatinib in a localized unresectable GIST had already been provided and it is consistently proposed by all available guidelines [12,13]. The Radiation Therapy Oncology Group (RTOG) was a prospective phase II study (RTOG 0132) evaluating safety and efficacy of neoadjuvant imatinib for patients with locally

advanced primary GIST (response was 7% partial, 83% stable, complications of surgery and imatinib toxicity were minimal), this approach is feasible [6].

Because rectal GISTs are rare, little date are available. Dematteo RP et al. describe the poor outcome of colorectal GIST compared with gastric or small bowel tumors [14]. Furthermore, because rectal GIST are often large tumors, resection can be difficult. In general, the resectability of a large tumor is hard to standardize and often considered surgeon dependent. The indication of a neoadjuvant imatinib therapy for locally large GIST hopes to become universally acceptable resection. In the case of rectal GIST using imatinib as a neoadjuvant therapy, there were particularly only few cases (one of 30 cases in RTOG 0132 trial [6], 4 of 15 cases in Fiore et al. [5]). Only a few case reports have described using imatinib as a neoadjuvant therapy for rectal GIST [15-19], and all case reports underwent complete surgery after downsizing of tumor. Similar surgical managements following neoadjuvant therapy have been described in the report of 3 patients [7] and 9 patients [8]. The neoadjuvant imatinib therapy might increase an opportunity of complete resection and moreover preserve function. In our cases, all patients underwent complete surgical resection macroscopically and microscopically including one complete response case, avoiding a radical excision and preserving the anus.

The optimal duration of preoperative imatinib for patients with locally advanced GIST is unknown. Median time to secondary progression during primary treatment with imatinib has been shown to be approximately within 10 months to 2 years [2,4,20]. The median time to best response in all responding patients was about 4 months (107 days), and most responses happened in 9 months of treatment [4]. Therefore, it seems quite reasonable to place surgery around 1 year from treatment start [21,22]. Several reports described that patient received surgery after 1.5 - 3 months of

neoadjuvant therapy [7,15,17-19]. Verweij J et al. recommend that studies on neoadjuvant therapy should be designed with a duration of treatment ranging from 4 to 6 months [4]. Because complete pathological response of pelvic GIST was obtained after 12 months with imatinib as neoadjuvant therapy, they could be extended up to one year [16]. In our cases, surgery was placed after 4-12 months of treatment. Since resistance relevant secondary mutation may be observed after neoadjuvant imatinib therapy, the time elapse with preoperative imatinib therapy should be chosen as short as complete resection can be carried out.

Laparoscopic surgery becomes increasingly feasible not only for abdominal surgical procedures but also for thoracic and soft tissue procedures. Laparoscopic surgery is minimally invasive and useful for the treatment of a rectal tumor [9,10]. Few reports have been published on the potential benefits of laparoscopic surgery for rectal GIST [17,19]. Our cases presented here underwent a laparoscopic surgery and the resection margins were macroscopically and microscopically not involved by residual tumors. Although rectal surgery generally presents major technical difficulties, a magnified view obtained by laparoscopy provides more precise image of dissection. Laparoscopic surgery is also advantageous in sufficiently mobilizing the lower rectum from the pelvic floor with good view, and even the dissection of the intersphincteric groove can be performed exactly. Laparoscopic ISR would be beneficial to patients concerning the oncological quality of operation [10]. When the rectal dissection is laparoscopically performed until the level of intersphincteric groove, the transanal intersphincteric dissection and pull the tumor from anus, and then complete resection could undergo with certain safety margin under a direct-view. This approach has advantages for large GIST, including the possibility of obtaining more safety margin than transanal approach, and preserving function of anal sphincter avoided permanent

stoma. Although transanal local resection approach is effective in small GIST less than 1 cm, it is unsuitable for large GIST. Furthermore, transanal local resection approach is difficult to secure an appropriate resection margin when GIST contact with adjacent organs such as the prostate or the vagina. In our cases, microscopically the resection margin was not involved of residual tumors. The satisfaction of patients was good because preservation of quality of life and no recurrence occurred.

In conclusion, we reported that neoadjuvant imatinib therapy in locally advanced rectal GIST is safe and effective, and shrinkage of tumor is expected with a clear benefit for the local treatment. It is often reasonable to consider a possible combination of imatinib therapy and surgical resection, especially laparoscopic ISR for minimally invasive surgery with preservation of the anus. However, we admit that this study includes a small number of case, we recommend combination of neoadjuvant imatinib therapy and laparoscopic ISR for locally advanced rectal GIST.

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Figure Legends

Figure 1: Magnetic resonance images obtained before (A-1, A-2) and after (B-1, B-2) treatment with imatinib therapy (Case 1).

Figure 2: Magnetic resonance images obtained before (C-1, C-2) and after (D-1, D-2) treatment with imatinib therapy (Case 3).