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Huge Pelvic GIST Got Good Control after Resistance to Tyrosine Kinase Inhibitors by SIB-IMRT: A Case Report and a Review of Literature

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Abstract

Purpose: Gastrointestinal stromal tumor (GIST) has been considered radiation-resistant and data on the radiotherapy for GIST in previous studies are lacking. The purpose of this article is to accumulate more experience in the application of radiotherapy for GISTs. **Materials and methods:** Review our own case material and the relevant English literature. **Results:** A huge pelvic GIST after resistance to tyrosine kinase inhibitors (TKIs) has been well controlled by simultaneous-integrated boost intensity-modulated radiation therapy (SIB-IMRT). The time from the initial shrinkage of the mass and subsequent stabilization to now was more than 18 months. The patient was palliated from the series of symptoms caused by tumor compression and well tolerated to the adverse reactions by radiotherapy. And the previous studies have shown that GISTs had a certain sensitivity to radiotherapy. **Conclusion:** SIB-IMRT may provide a new means of achieving objective response and prolonging survival in selected GIST patients.

Keywords

Gastrointestinal Stromal Tumor, Radiotherapy, Resistance, Tyrosine Kinase Inhibitors

1. Introduction

Gastrointestinal stromal tumors (GISTs) are relatively rare, with an annual incidence of approximately 10 per million population, generally owing to mutations in one of two receptor protein tyrosine kinase genes: KIT or platelet-derived

growth factor receptor A (PDGFRA) [1]-[4]. The primary treatment is complete surgical resection for local GISTs, and tyrosine kinase inhibitors (TKIs) are the recommended options for recurrent, metastatic or unresectable patients [5] [6]. However, it is well-known that about 40% to 50% of GISTs will have cancer recurrence after surgery and all TKIs will show resistance [7]. Therefore, the post-resistance treatment is still an important factor affecting the survival of patients.

In the past, GISTs were not considered to be sensitive to radiotherapy, coupled with the poor tolerance of surrounding normal organs to traditional radiotherapy techniques, thus radiotherapy rarely used in GIST patients. With the development of radiotherapy technology, some studies have attempted to apply radiotherapy for palliative purposes in advanced GISTs and have achieved some curative efficacy, indicating that GISTs are not generally resistant to radiotherapy.

In this article, we report a case of an advanced GIST patient who progressed after second-line targeted therapy. The results showed that the irradiated lesions continued to decrease and the clinical symptoms palliated completely after simultaneous-integrated boost intensity-modulated radiation therapy (SIB-IMRT). The study also reviewed relevant literature focusing on radiotherapy for GISTs.

2. Case Report

In October 2011, a 62-year-old man suffering from abdominal discomfort underwent CT examination and found a huge abdomen mass. The completely local resection and anastomosis of small intestine were performed, and histopathology confirmed the diagnosis of GIST. The histology report specified GIST of the ileum (maximum diameter: 18 cm, mitotic index: >5/50 HPF). Tumor genotyping with sequencing for mutations in KIT (exons 9, 11, 13 and 17) and PDGFRA (exon 18) disclosed a mutation at exon 11 of the KIT gene. Taking account of the high risk of recurrence, the patient was treated with imatinib at a daily dose of 400 mg which was stopped for family financial difficulties after one year. Periodic CT was scanned until pelvic recurrence in October 2013, then he took imatinib again. In November 2015, a mild increase in the size of lesion was detected, and the therapy was switched to the second-line treatment with sunitinib. After 7 months of sunitinib treatment, the volume of the lesion continued to increase (diameter 18 × 10 × 12.4 cm, CT value 71HU, **Figure 1(a)**), with the symptoms of poor appetite, distension, frequent urination and increased times in defecation. Regorafenib couldn't be obtained in China at that time. Therefore, the patient was transferred to our institution where multiple disciplinary teams of GIST regularly conducted. Due to the development of symptoms, the increase of the lesion volume and the lack of surgical options, we administered SIB-IMRT for the pelvic lesion in September 2016.

The gross target volume (GTV) was treated with 50.4 Gy delivered in 28 fractions (1.8 Gy every fraction, 5 fractions weekly). The area of 1.5cm isotropic erosion from the inter contour of GTV was treated with simultaneous-integrated boost (SIB) 60 Gy divided into 28 fractions. The area of 2.5cm isotropic erosion

from the outer contour of GTV was treated with SIB 62 Gy. The peripheries and lymphatic drainage of the gross tumor were not irradiated as the clinical target volume (CTV). The planning gross target volume (PGTV) encompassed the gross tumor plus the margin required by target movement and set-up errors, approximately 0.5 cm. The areas out of the planning target volume (PTV) get steep dose gradients and the highest dose in the areas out of the PTV was less than 50.4 Gy (Figure 2). The patient who obtained a clear response was well tolerated in general. The tumor was decreased in size and density (diameter 14 × 8 × 10 cm, CT value 63HU, Figure 1(b)), and the above symptoms were relieved completely. The major radiotherapy-related adverse event was mild diarrhea. Subsequent radiological examination recorded the continued shrinkage of the irradiated lesion after 12 months and 18 months from radiotherapy (Figure 1(c), Figure 1(d)). According to the Choi criteria, the patient was evaluated as partial response (PR). After radiotherapy, the patient refused systemic treatment in order to improve the quality of life due to the remission of symptoms. So far, the patient is generally in good control.

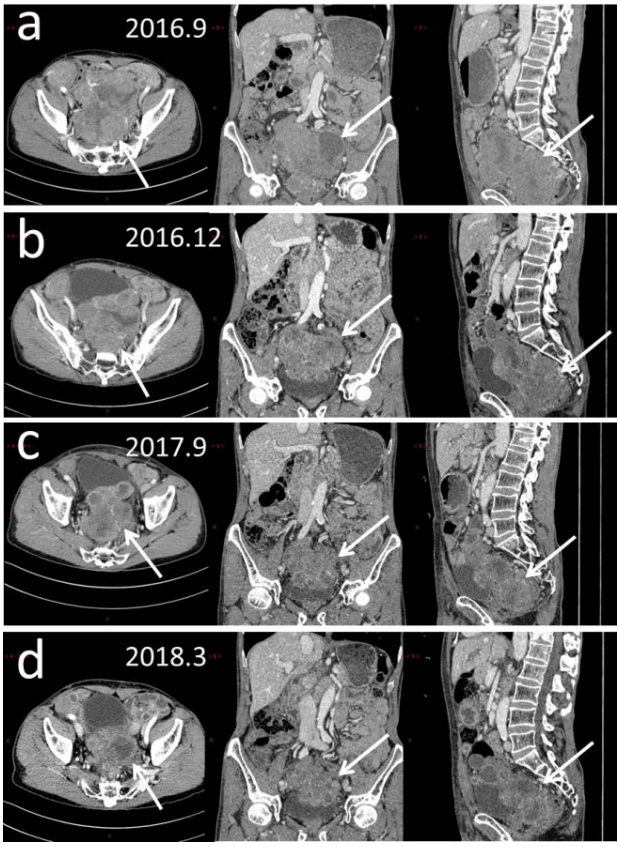

Figure 1. The changes in size and density of the tumor before and after radiotherapy. (a) The CT imagine of the tumor before radiotherapy (diameter 18 × 10 × 12.4 cm, CT value 71 HU). (b) The CT imagine of the tumor 3 months after radiotherapy (diameter 14 × 8 × 10 cm, CT value 63 HU). (c) The CT imagine of the tumor 12 months after radiotherapy (diameter 12 × 6.5 × 7.8 cm, CT value 59 HU). (d) The CT imagine of the tumor 18 months after radiotherapy (diameter 9.5 × 5.3 × 7.5 cm, CT value 50 HU).

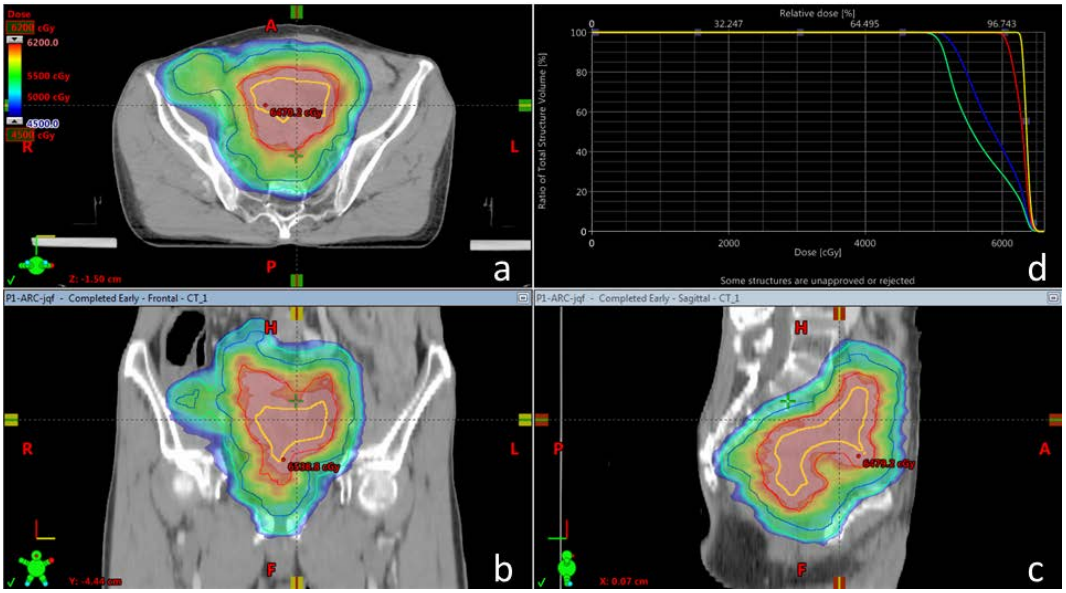

Figure 2. Radiotherapy dose profile. Image of a dose distributions of an axial plane (a), coronal plane (b) and sagittal plane (c) in color wash and the Dose volume histogram (d), The yellow contour is 2.5 cm isotropic erosion from the inter contour of GTV; the red contour is 1.5 cm isotropic erosion from the inter contour of GTV; the blue contour is GTV; the green contour is PGTV.

Table 1. Characteristics of previous literature.

References	Sample size	Primary tumor site	Radiotherapy site	Radiotherapy technology	Dose (Gy)	Fractionation schemes (cGy × Fx)	Results
Jacqueline 2001 [20]	10	the small intestine	pelvis	external radiotherapy	median dose: 45	180 × 25	All patients subsequently relapsed. In six cases, relapse was outside the radiation field.
Boruban 2007 [21]	1	pelvic	pelvis	external radiotherapy	54	200 × 27	CR*
Cristian 2011 [14]	1	ileum	left supraclavicular mass	external radiotherapy	50	200 × 25	The mass shrinked from 56 × 39 mm to 44 × 31 mm.
L. Gatto 2017 [22]	1	Stomach	paracaval mass	external radiotherapy	35	250 × 14	The mass shrinked from 130 mm to 80 mm.
John 2013 [17]	22	NR	abdominal (4 tumors), vertebral (11 tumors), pelvis (3 tumors), hip, peritoneum, liver (2 tumors)	conventional opposed photon fields (13 tumors), IMRT (9 tumors)	-	300 × 10 (n = 8), 180 × 25, and 200 × 25, SBRT: 2400 × 1 (n = 2); 900 × 3, (n = 2); 800 × 3, (n = 1); 600 × 5 (n = 2); and 500 × 5 (n = 2)	The 6-month PFS and OS were 57.0% and 57.8%.
Heikki 2015 [15]	25	Stomach (n = 6), Small intestine (n = 13), Colon/rectum (n = 3), Other (n = 3)	intra-bdominal (n = 21), liver metastases (n = 4)	3DRT (n = 18), IMRT (n = 7)	median PTV dose: 39.6 (range from 30 to 40)	180 - 200 daily fractions, 5 fractions weekly	DCR: 88%. The median time to radiotherapy target lesion progression was 4-fold longer than that at any site (16 versus 4 months).
L. Gatto 2017 [22]	1	Stomach	mass below the diaphragm	cyberknife	45 + 40 (after 60 days)	900 × 5 + 1000 × 4 (after 60 days)	The tumor is stable in size, but there is a decrease in hypervascularity.
Pollack 2001 [23]	1	rectum	pelvis	opposed anteroposterior field	50.4	NA	No progression was noted for 2 years.

OS: overall survival; PFS: progression-free survival; CR: complete response; DCR: disease control rate; NA: not available; SBRT: stereotactic body radiation therapy, defined as hypofractionation of ≥500 cGy per fraction image guidance for delivery; IMRT: intensity modulated radiation therapy; 3DRT: 3-dimensional radiotherapy. *: The pelvic lesions completely disappeared 27 months after radiotherapy.

Radiotherapy for Gastrointestinal Stromal Tumors in previous studies: In addition, a thorough review of the English literature (PubMed search) was conducted including large consecutive series and relatively small case series focusing on radiotherapy for GISTs. Some basic features were summarized (**Table 1**), containing the characteristics of tumors, the area, dose and segmentation model of radiotherapy.

3. Discussion

TKIs are the preferred treatment of advanced or unrespectable GISTs, which have improved the overall survival [8] [9]. Nevertheless, resistance to all the available TKIs presents a huge challenge for the management of advanced GISTs. According to a pivotal study of imatinib for advanced GISTs, 10% - 15% of patients showed primary resistance and 40% - 50% developed secondary resistance after about 24 months of treatment [10]. Sunitinib and regorafenib, the second and the third approved drugs, also develop resistance in a short time, and the toxicity is more serious compared to imatinib [11]. Novel inhibitors are currently under investigation to overcome the effect of resistance mutations. However, there is no obvious breakthrough in the mode of treatment after drug resistance.

Radiotherapy has been less commonly considered in GISTs, which can be attributed to the two points: 1) GISTs were considered to be insensitive to radiotherapy; 2) GISTs mainly metastasize to peritoneum and liver, these metastatic sites are poorly tolerated for traditional radiotherapy.

In recent years, with the development of radiotherapy techniques, some clinicians tried to use radiotherapy and achieved certain curative effect, which indicates that the role of radiotherapy in GISTs may be underestimated [12] [13]. Lolli reported a successful radiotherapy for the control of supraclavicular metastasis in a case of ileum GIST, who developed rapidly progresses after ileal resection and took multi-line targeted drugs [14]. After receiving radiotherapy (50 Gy divided into 25 fractions, 5 fractions weekly), the supraclavicular lesion was reduced from 56 × 39 mm to 44 × 31 mm and the symptoms of pain and difficulty in swallowing were significantly palliated. A Phase II clinical trial was reported in 2015, in which 25 GIST patients with intra-abdominal or liver metastases were treated with radiotherapy [15]. The median cumulative PTV dose was 39.6 Gy with well tolerance. The clinical benefit rate (complete response (CR), PR, or stable disease (SD)) were 88%, and the median progression time for irradiated sites was 16 months that is four times longer than progression time for any sites. This trial concluded that most GIST patients with local lesions could be steadily controlled by radiation therapy and metastases had a certain sensitivity to radiation. Turkish Ozkan analyzed the literature of radiotherapy in rectal GISTs [16]. He demonstrated that GISTs were radiosensitive for the long-term local control and most patients could benefit from radiotherapy with palliative, adjuvant or definitive intent. And our case also showed that GISTs were not generally resistant to radiotherapy, which was consistent with previous studies. In short, radiotherapy can largely relieve

clinical symptoms and improve local control rates at tolerable dose in GISTs.

We could observe that, in previous studies of radiotherapy in patients with GISTs, lesions were often administered with a total dose of about 40 Gy in the conventional fractionation mode and got stabilization for only months. And low radiation dose may be one of the reasons for the poor efficacy of traditional radiotherapy. Cuaron et al. reported a retrospective study of radiotherapy in 15 patients with advanced GISTs after targeted failure [17]. In their study, patients received radiotherapy at different doses and fractions, most commonly 30 Gy in 10 fractions. Finally, 53% of tumors reached SD. The rate of PR in patients treated with stereotactic body radiation therapy (SBRT, defined as hypofractionation of ≥500 cGy per fraction) was 63%, thus the author indicated that GISTs were more sensitive to a higher fraction dose. In our report, the lesions center dose can reach about 62Gy by SIB-IMRT, making the lesions significantly continued to shrink. With the advances in new radiotherapy techniques such as IMRT, image-guided radiation therapy (IGRT), and SBRT, the target bioequivalent dose may be significantly increased under the premise of the maximum protection of normal tissues. But the best suitable dose for GISTs also needs further explorations.

Table 2. Tumor size and efficacy in three reports.

References	John 2013 [17]															Cristian 2011 [14]	L. Gatto 2017 [22]
Tumor size (mm)	SPD															max diameter	
	1.2	4.14	4.44	6.24	8.94	12.22	15.12	24.91	26.95	50.95	81.78	94	118.3	120	142.3	56 × 39	130
Dose of RT (cGy × Fx)	500 × 5	900 × 3	800 × 3	300 × 10	2400 × 1	900 × 3	2400 × 1	600 × 5	500 × 5	300 × 10	300 × 10	300 × 10	200 × 25	180 × 25	300 × 10	200 × 25	250 × 14
RECIST	PR	PR	SD	SD	PR	PR	SD	PR	PD	SD	SD	SD	SD	PD	PR	PR	PR

SPD: sum product diameter; PR, partial response; SD, stable disease; PD, progressive disease; RECIST: response evaluation criteria in solid tumors.

Large GISTs can also be well controlled by radiotherapy. The large volume of the tumor is one of the reasons for an incomplete operation. Without the help of the TKI, an incomplete operation may lead to an acceleration regrowth in local or an extensive spread to other areas. Different from operation, radiotherapy can suppress the growth of the tumor for a long time even if the dosage is not enough to radically kill the tumor. Meanwhile, larger GISTs tend to be more fixed, especially in pelvic cavity, where the tumor has little space to move and is far away from the diaphragm, which creates a good condition for radiotherapy. Furthermore, a high dose can be given in the tumor center area by the SIB-IMRT radiation therapy. It can avoid the radiotherapy tolerance induced by hypoxia in tumor central region, while organs at risk are irradiated at a safe dosage. In our report, the escalation-gradient dose distributed from outside to the center of tumor by SIB-IMRT, making the lesions significantly continued to shrink. But from the previous report, we found that the smaller lesions seemed to get better control (**Table 2**) [17]. The probable reason is the radiotherapy tolerance induced by hypoxia in tumor central region. Li *et al.* reported that SIB-IMRT offered an increasing dose distribution gradient from the peripheral to the center of the tumor while spared

rectum and bladder from the high dose region, thus large GISTs could get similarly good control like small ones with the SIB-IMRT [18].

The radiation area for GISTs may include the tumor itself only. The GISTs rarely cause fatal metastasis in the brain or lungs, and the recurrence is mainly concentrated in the abdominopelvic cavity, thus controlling the tumor in the abdominopelvic cavity can lead to a good prolongation of the survival time. The nodal metastasis in GISTs is also very rare. The overall frequency of nodal metastasis in GISTs was approximately 1% - 4% in previous studies [19]. Therefore only the gross tumor but not the lymphatic drawing region need irradiation. In our case, although the peripheries and lymphatic drainage of the gross tumor were not irradiated as the CTV in order to reduce the damage of normal tissue and vital organ, there was still no recurrence in the surrounding areas of the tumor for more than 18 months. It suggested that the radiotherapy area in GISTs may only contain the gross tumor. It could significantly reduce the range of irradiated area and ensure a good tolerance in normal gastrointestinal tract.

Despite the fact that some patients with GISTs have acquired efficacy through radiotherapy and the view of resistance to radiotherapy has changed, these studies are most case reports or retrospective analysis. So there are many problems still need to be explored: radiotherapy indications, benefiting people, dose, segmentation, combined with TKI and so on.

4. Conclusion

More and more research has broken the outdated concept that GISTs are not sensitive to radiotherapy due to the certain curative effect achieved, which provides a basis for further application of radiotherapy in GISTs. Although surgery and targeted therapy remain the standard treatment, we believe radiotherapy may provide a new means of achieving objective response and prolonging survival in advanced or selected GISTs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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