Review Article

Radiotherapy for Gastrointestinal Stromal Tumors

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Abstract

Objective: Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors of the gastrointestinal tract, which frequently cause intraabdominal metastases. The current standard of care is surgery for localized cases, and adjuvant imatinib is recommended for tumors with a high risk of recurrence. To date, radiotherapy has not been commonly accepted as a part of multimodality treatment approach other than palliation. However, recently published case reports and some small series suggest that radiotherapy is a valuable option for controlling locally progressive, drug-resistant disease. The aim of this review is to provide a viewpoint from a radiation oncologist concerning the management of GISTs, especially rectal GIST, and clarify the role and technical aspects of radiotherapy in the treatment approach.
Data Sources: A comprehensive search in PubMed using the keywords "radiotherapy for rectal GIST" and "rectal GIST" was undertaken. The literature search included the related articles after 1995.
Study Selection: The main articles including rectal GIST case reports and GIST series containing rectal cases were the primary references.
Results: Surgery is the mainstay of treatment. However, to date, radiotherapy is included in the multidisciplinary treatment strategy of rectal GISTs in some circumstances with palliative, adjuvant, or definitive intent using different treatment doses and fields.
Conclusions: Recently reported long-term local control rates indicate that GIST is a radiosensitive disease. This makes radiotherapy a valuable alternative in GIST management with curative intent, especially in patients who (1) cannot tolerate or are resistant to chemotherapy agents, (2) have an unresectable disease, (3) have a gross or microscopic residual disease after surgery, and (4) have a recurrent disease.

Key words: Gastrointestinal Stromal Tumor; Radiotherapy; Rectum

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. They are identified as a different entity from other sarcomas, arising from the interstitial cells of Cajal or their precursors.[1,2] Size and mitotic activity is reported to be the most important factors for the risk estimation in terms of the malignant behavior of GIST according to the National Cancer Institute consensus classification.[3-5] Location is added as a prognostic factor, and in more recent classification systems,[6,7] GIST at different locations in the gastrointestinal system necessitates different therapeutic approaches. Surgery with the R0 resection of tumor is recommended as primary treatment in nonmetastatic cases.[3,4] Most of the GIST cases carry *KIT* gene mutations, resulting in uncontrolled cell proliferation via the constitutive activation of KIT kinase activity. Therefore, imatinib, an inhibitor of KIT that is a platelet-derived growth factor-α (PDGFR-α), came into use as the standard first-line agent for metastatic GIST[1,2] and sunitinib is used for patients who are imatinib refractory.[8] Radiotherapy is not recommended as a treatment modality in the current treatment guidelines[1] and is only used with palliative intent for bone metastases.[2] This approach is based on previous reports that suggest that radiotherapy is not beneficial in the treatment of GIST[9] while it is considered a radiotherapy-resistant or minimally responsive entity.[10-13] However, the results from a few case reports[14] and some retrospective data[15] reported that GIST is not uniformly radioresistant and may benefit from radiotherapy.[16]

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Approximately 5% of all GIST cases arise in the rectum,[17-19] and it has been reported that rectal GIST had higher rates of metastatic potential before imatinib was introduced to clinical practice.[6,7] Sphincter preservation is another important part of rectal GIST treatment;[20-23] however, the lack of date in the literature makes rectal GIST a challenging entity. Treatment with adjuvant imatinib lowers the risk of relapse.[3,4,24] Neoadjuvant administration with the intent of reducing the tumor volume improved rates of R0 resections,[21] and even in small retrospective series, improvement in disease-free survival (DFS) and overall survival (OS) has been determined and compared to upfront surgery.[25,26] When the metastatic potential was evaluated with a site-related intent, more than 50% distant relapse was reported in rectal GIST patients if the number of mitoses per 50 high-power fields (HPFs) was more than 5 or the tumor size was more than 5 cm.[7] However, all the data mentioned above belonged to the preimatinib era.[25]

This review aimed to take a closer look at the role of radiotherapy in the treatment of GIST, especially rectal GIST, and elaborate on radiation therapy in terms of indications, dose, fractionation, and treatment fields.

Prognostic Factors

Size and mitotic activity are the most frequently reported factors used to estimate the risk of malignant behavior of GIST and are confirmed by the National Cancer Institute consensus classification.[3-5]

Miettinen and Lasota found distant metastasis in more than 50% of patients with rectal GIST who had more than 5 mitoses per 50 HPF or with tumor size larger than 5 cm,[7] whereas other studies reported that on the contrary, tumor size could not be considered as a prognostic factor for rectal GIST.[27]

In certain reports, rectal GIST is classified into two risk groups where low-risk group refers to tumors smaller than 5 cm and exhibiting fewer than 5 mitoses per 50 HPF and the high-risk group includes patients with tumors of 5 cm and more or exhibiting more than 5 mitoses per 50 HPF or both.[25,28] Hohenberger and Eisenberg additionally concluded that low-risk GIST may not benefit from adjuvant treatment if resected with clear margins; however, for high-risk lesions, adjuvant therapy must be considered.[28]

A third prognostic factor in more recent classification systems is considered as the location of GIST.[6,7] According to the clinical data presented by Wang *et al*., the relapse-free survival (RFS) time of small rectal GISTs was significantly different than that in other anatomic sites. The authors demonstrated that there was an increased degree of malignancy and recurrence rate in rectal GISTs.[27] DeMatteo *et al*. also reported a poorer outcome of colorectal GIST compared to nonrectal counterparts.[6]

The approval of imatinib dramatically changed the treatment options and prognosis for GIST. Henceforth, insufficient adjuvant imatinib is also considered as a factor independently associated with poor prognosis in addition to a high mitotic count, rectal location, large size, and rupture.[29-31] Complete resection is warranted for local disease control. Perioperative imatinib was associated with improved outcome in terms of DFS and OS ($P < 0.01$, and $P = 0.03$, respectively), which might be attributed to improved surgical margins with preoperative imatinib.[25]

In a surgical series of 21 patients with rectal GIST, mitosis, a positive resection margin and open surgery, was reported as a poor prognostic factor supported with lower DFS of the open surgery group compared with the local excision group.[21]

Most GIST cases (85–90%) have *KIT* gene mutations, which result in uncontrolled cell proliferation via KIT kinase activity. A smaller proportion (5–8%) carry mutations in PDGFR-α.[1-4]

General Treatment Considerations

Surgical resection is considered as the standard of care for nonmetastasized GIST. Current guidelines recommend wide resection with negative margins.[3,4] Most rectal GISTs were suitable for local excision[32-34] and some of primary GIST patients were cured by surgery alone.[35,36] Local removal may be performed by transanal, transsacral (Kraske), or transvaginal approach.[37-39] Liu *et al*. suggested that transanal resection is adequate for rectal GISTs located closer than 5 cm to the anus.[21] Unlike rectal cancer, the surgical principles for rectal GISTs do not comprise lymph node dissection or total mesorectal excision;[26] however, the complete removal of the tumor-bearing rectal wall and a tumor-covering tissue layer must be achieved when GIST originates from the muscularis propria and a negative surgical margin and complete resection are warranted.[32-34] DeMatteo *et al*. reported a higher rate of local recurrence in cases with positive margins and they recommended re-excision when feasible.[40,41] However, surgical indications and timing of surgery for GISTs with a diameter of <2 cm are still controversial.[42]

Peritoneal metastases in GIST can be seen due to intraoperative tumor cell contamination and a higher risk can occur after transabdominal resection, which destroys the integrity of the peritoneum. Therefore, some authors highlight the importance of presurgical biopsy, histological evaluation, and staging. They rationalize this suggestion based on the extraluminal growth of most rectal GISTs not being clearly revealed by endoscopic inspection. Thus, cross-sectional imaging is mandatory.[40,41] Pretreatment biopsy, detailed local staging, and c-kit mutation analysis are also important determinants for treatment planning in terms of surgical or adjuvant therapy.

Imatinib mesylate is the primary treatment at the onset of the disease in patients with recurrent, metastatic, or unresectable GISTs.[29-31] Long-term imatinib may be administered until progression in unresectable patients. Cytoreductive surgery alone for recurrent, metastatic, or unresectable GISTs

is not recommended.[29-31] Adjuvant imatinib mesylate is now recommended when there is a significant risk of recurrence.[35,36]

Neoadjuvant imatinib in rectal GIST has been shown to improve the rates of complete resection as well as local DFS and OS.[25,26] Wang *et al*. also reported this novel agent as a safe and effective neoadjuvant therapy for rectal GISTs with a higher rate of local excision and function preservation.[27] Patients with a complete/partial response or a stable disease based on the Choi criteria after preoperative imatinib may be candidates for surgery.[29-31] Neoadjuvant imatinib was also a suitable alternative for patients who needed multivisceral resection for a complete resection or smaller tumors at critical sites (e.g., supraanal localization with sphincter involvement).[28] If a sufficient tumor shrinkage is achieved after neoadjuvant treatment, even laparoscopic surgery may be an option.[43] Some authors also advocated preoperative treatment with imatinib and subsequent surgery in metastatic GIST.[32-34]

The optimal duration of neoadjuvant therapy for sphincter preservation is still a controversial issue. One of the strongest challenging topics is secondary mutations and the predisposition toward disease progression with extended periods of neoadjuvant imatinib.[22]

Radiotherapy Indications

Previously, radiotherapy was not considered as a suitable option for GISTs due to the requirement of large abdominal fields causing small bowel toxicity and resulting in a low therapeutic ratio. However, to date, radiotherapy is included in the multidisciplinary treatment strategy of GISTs in certain circumstances. As adjuvant to surgery, radiotherapy could potentially limit the development of resistance to imatinib. Preoperative administration with or without imatinib is another indication for tumors at high risk of local recurrence or R1 resection. Neoadjuvant radiotherapy helps achieve an increased rate of normal tissue sparing and safer dose escalation. Radiotherapy can also be used as a local treatment for tumors that develop in duodenal or esophageal locations where resection could cause functional problems. In locally progressive or metastatic GISTs, even short courses of radiotherapy are shown to be effective for the palliation of local symptoms with reasonable toxicity.[15,44-46]

Dose

In general, conventional fractionation and modest cumulative doses are recommended in radiation planning for GISTs, but other fractionation schemes have also been investigated depending on treatment objective. Cuaron *et al*. reported that patients were most commonly treated after tyrosine kinase inhibitor (TKI) failure. In their study, radiation therapy was delivered with 300 cGy × 10, 180 cGy × 25, and 200 cGy × 25 fractions in the patients treated conventionally. Stereotactic body radiation therapy was used for 9 tumors (2400 cGy × 1, n = 2; 900 cGy × 3, n = 2; 800 cGy × 3, n = 1; 600 cGy × 5, n = 2; and 500 cGy × 5, n = 2). Conventional-opposed photon fields were used in 59.1% of patients, and intensity-modulated radiotherapy (IMRT) was used for nine tumors (40.9%) in the abdomen, pelvis, and paraspinal region. The partial radiographic response and the 6-month local progression-free survival were found to be 35% and 57%, respectively. The radiographic response of the patients treated with 5 Gy fraction dose was 63%, and the authors concluded that GISTs are more sensitive to a higher fraction dose.[15]

A small series of nine patients with incompletely resection of GIST reported local control in six patients treated with 45–60 Gy of radiation.[47] Radiotherapy, combined with imatinib, resulted in a reduction in tumor size of a large rectal GIST and allowed sphincter-sparing surgery with a dose of 50.4 Gy, which was considered adequate for a pathologic complete response.[48]

In a case with a recurrent stomach GIST, a dose of 35 Gy was administered in 14 fractions. An objective response in the paracaval mass and pain relief was achieved without any complications.[49] Another case was reported in which the patient underwent 50.4 Gy postoperative radiation following a R1 resection of a 7-cm rectal GIST. Two years later, the patient had remained free of disease.[50] Knowlton *et al*. presented a case study in which 20 years of local control was reported in a 37-year-old man with an unresectable and nonmetastatic GIST treated with debulking surgery and 36 Gy radiotherapy.[51] A few case studies advocated concurrent radiotherapy and TKIs. The radiation treatment of 50 Gy to metastatic site with sorafenib resulted in a clinical and radiographic response.[52] Similarly, a large incompletely resected pelvic mass had a complete response followed by durable local control with concurrent radiation and imatinib despite the progression of liver metastasis.[53] These similar results on local control and progression in metastasis gave rise to the suggestion that radiation helped eradicate resistant clones. Selective internal radiotherapy with 90Y microspheres has been advocated in anecdotal cases.[36] In conclusion, GIST metastases are moderately radiosensitive and the response is durable with radiotherapy.

Treatment fields

In the previously published cases or small series, no detail about radiotherapy fields is encountered. The treatment of GIST was reported to be challenging using abdominal fields since this caused toxicities in small bowel and visceral structures. In the current era of technological development of IMRT and image-guided radiotherapy, the treatment of abdominal diseases results in lower acute and delayed toxicity with more normal tissue protection allowing dose escalation.[53]

In a case of GIST of the antrum following a small intestine excisional biopsy of a mass in the antrum, radiotherapy was administered to the area of disease, including most of the stomach with a 1.5 cm margin to 36 Gy in 24 fractions of 1.5 Gy each with anteroposterior/posteroanterior fields. Radiotherapy was well tolerated with no late toxicity.[51]

Cuaron *et al*. used conventional-opposed photon fields in 59.1% of patients and IMRT was used for nine tumors (40.9%) in the abdomen, pelvis, and paraspinal region.[15]

The total treatment plan, treatment field, and position used in rectal GIST radiotherapy were reported in detail by Pollock *et al*.[50] in a case that was treated in a frog-legged position to protect tissues at risk. Rectal contrast and an anal marker were used for accurate determination. The first 36 Gy was delivered to the whole pelvis from the lumbosacral junction as the superior border to 4 cm inferior to the anal verge. The second phase of the treatment was 9 Gy to a partial pelvic field with the superior border shrinking to the base of the sacroiliac joints. Anteroposterior-opposed field arrangement was used with customized blocking. The pelvic and perirectal lymph nodes were included where lateral inguinal lymph nodes were excluded while no evidence of involvement was detected in a physical examination or computed tomography (CT) scan, which suggested that there was a low risk of occult disease. A final phase of 540 cGy was delivered to the volume determined by a contrast study. The margins were 2 cm on the CT-based tumor volume.[50]

The two main metastatic routes of GIST are through intraperitoneal dissemination and the liver; however, metastasis to other visceral organs is rare.[54] The incidence of lymph node metastasis in GIST patients is a very important determinant for field design. Although a number of cases have been reported, lymph node metastasis is also unusual (1–2%);[55-61] therefore, routine lymphadenectomy is not recommended.[9,40,62,63]

In a series of 29 patients with GIST, lymph node metastasis was investigated retrospectively in positron emission tomography-CT database with the finding that the incidence was 20.7%. Other than stomach or small bowel, 4 of the 5 adult metastatic patients had a primary tumor at very rare sites and this was statistically significant ($P = 0.004$).[64] The incidence of lymph node metastasis in gastric GISTs was also very low; however, the actual incidence is still a matter of debate due to the limited number of lymph node dissection. In 57 patients who underwent R0 resection, lymph node metastasis was reported as 8.8%.[65] The published case reports[43,48,50,66-69] and series[15,23,25,27,70-74] are summarized in Supplementary tables 1 and 2, respectively, in terms of management modalities used, details of the surgical procedure, radiotherapy treatment doses and fields, and outcomes if available. Taking the literature into consideration, although there is no accepted guideline, elective lymph node irradiation can be omitted in rectal GIST cases.

Toxicity

Radiotherapy is usually well tolerated; however, imatinib enhances sensitivity to radiotherapy.[75] In a report by Yuasa *et al*., diarrhea, nausea, and fatigue were recorded in 13 (52%), 9 (36%), and 8 (32%) patients, respectively during or after radiotherapy. Anemia was frequently recorded but attributed to advanced GIST and TKI therapy rather than radiotherapy. TKIs that inhibit the vascular endothelial growth factor receptors may cause recall reactions[76] to radiotherapy and bleeding[77] at the irradiated sites. On the contrary, a few Phase I and II trials suggested that concomitant sunitinib and radiotherapy is safe.[78,79] In a recent Phase II study with sorafenib both concomitantly and after radiotherapy in advanced hepatocellular carcinoma, 35% of the 40 patients treated developed >2 grade hepatotoxicity and 15% had >3 grade hepatotoxicity.[80] Radiotherapy appears to be well tolerated in patients who have GIST progressing at one or a few sites treated with palliate intent. Before the imatinib mesylate era, 29 cases of rectal GIST (KIT-positive) had been reported for the treatment of GISTs in Japan. None of them was treated with radiotherapy.[67]

Conclusions

Conclusively, radiotherapy has not been preferred as one of the modalities in the general management of GIST. This limited use can be attributed to the pattern of metastasis in GIST and radiotherapy has been restricted for palliative intent in previous reports.[44,45] Recently reported long-term local control indicates that GIST is radiosensitive, which is contrary to common belief. This might make radiotherapy a valuable alternative in GIST management with curative intent, especially in patients who (1) cannot tolerate or are resistant to TKI agents, (2) have an unresectable disease, (3) have a gross or microscopic residual disease after surgery, or (4) have a recurrent disease.[66]

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Rectal GIST cases in the literature

References	Age (years)/ gender	Localization and volume	Surgery	Chemotherapy	Radiotherapy	Follow-up
Somu *et al*. 2016[66]	66/male	3 cm from the anal verge in the right lateral rectal wall 6.3 cm × 5.4 cm × 6.7 cm	Laparoscopic excision	Adjuvant imatinib	None	NA
Ciresa *et al*. 2009[48]	54/male	Lateral-right rectal wall extending to the anal canal/4.7 cm × 4.0 cm	Patient underwent a sphincter-saving surgical procedure (low anterior resection)	Neoadjuvant imatinib	50.4 Gy 1.8 Gy/day Box or 3-field 3D conformal	NA
Kyo *et al*. 2016[43]	46/male	8 cm in maximum diameter, anterior wall of the lower rectum	Laparoscopic low anterior resection with total mesorectal excision, coloanal anastomosis, and diverting ileostomy	Neoadjuvant imatinib treatment	None	Alive and disease-free 37 months after surgery
Hamada *et al*. 2008[67]	60/male	3.0 cm recurrent tm	Fourth excision operation was performed with a perineal approach	Neoadjuvant imatinib treatment	None	Alive and disease-free 42 months after last surgery
Tazawa *et al*. 2017[68]	75/female	5.3 cm × 4.2 cm, behind the rectum	Partial sphincter saving rectal resection with creation of an ileostomy	Neoadjuvant imatinib treatment	None	No evidence of disease in the 2-year follow-up
Pollock *et al*. 2001[50]	77/female	2–3 cm left anterior rectal wall, 1–2 cm above the dentate line	Transanal excision and a 7-cm mass was removed. Margins were equivocal so excess redundant mucosa was excised	None	36 Gy whole pelvis. Additional 9 Gy to partial pelvic field. Final 540 cGy to a field determined by a contrast study. The margins 2 cm to CT-based tumor volume	2-year CT scan revealed continued regression of the left anterior rectal tumor
Carlson *et al*. 2016[69]	51/male	6.5 cm × 6.0 cm rectal mass just proximal to the sphincter	APR	Neoadjuvant imatinib treatment	None	Metastasis to penis 3.5 years after APR

APR: Abdominoperineal resection; 3D: Three-dimensional; NA: Not available; CT: Computed tomography.

Supplementary Table 2: GIST series reported in the literature

References	Rectal GIST/ total, *n*	Surgery	Chemotherapy	Radiotherapy	Outcome
Terada 2009[70]	1/31	NA	Imatinib mesylate in 6 cases	NA	OS: 4 of 31 patients developed metastasis and died of disease; 27 alive without disease
Wang *et al*. 2015[27]	8/20	19/20 underwent R0 resection. 7 rectal GISTs, of which 3 had transanal local excision, 2 were excised with HAR, 1 was excised with Hartmann's procedure and 1 with Miles' procedure	1 rectal GIST patient received imatinib mesylate	NA	Follow-up: 49.5 months (range, 10.5–94.4 months) 5 patients had recurrence, of whom 4 had rectal tumors and 1 had an enterocoelial tumor
Cuaron *et al*. 2013[15]	1/15	NA	Sunitinib	300 cGy × 10 fractions (*n* = 8). Other schemes 180 cGy × 25, 200 cGy × 25. SBRT for 9 tumors (2400 cGy × 1, *n* = 2; 900 cGy × 3, *n* = 2; 800 cGy × 3, *n* = 1; 600 cGy × 5, *n* = 2; and 500 cGy × 5, *n* = 2). Three patients with a partial course of 300 cGy × 10	The median follow-up 5.1 months 12 of the 15 (80%) died. Among the 18 tumors that were symptomatic at presentation at least partial palliation was achieved in 17 (94.4%). completely palliated in eight tumors (44.4%) Partial radiographic response was seen in 35.3% (*n* = 6). Stable disease 52.9% (*n* = 9), progressive disease 11.8% (*n* = 2). Among tumors treated with SBRT partial response was seen in 62.5% (*n* = 5), stable disease was seen in 25.0% (*n* = 2), and progressive disease in 12.5% (*n* = 1). The estimated 6 months local progression-free survival was 57.0%, MS 6.6 months, estimated 6 months OS 57.8%
Kapoor *et al*. 2013[71]	1/49	NA	Imatinib/sunitinib	NA	3-year RFS 38%
Jakob *et al*. 2013[25]	39	36/38	Imatinib	None	Of 4 patients with metachronous peritoneal metastasis, 3 had undergone transabdominal surgery. Another patient with secondary peritoneal metastases had been treated with local excision (R1 at pathology). Three patients with secondary metastases died of disease at 18, 46, and 102 months after resection of the primary tumor. Of 36 patients who underwent resection for primary tumor, five developed local recurrences. Median time to recurrence was 12 months (range 2–70 months) from the date of surgery
Fujimoto *et al*. 2014[72]	5	Laparoscopic sphincter-preserving surgery after 4–12 months	Neoadjuvant imatinib treatment	None	No recurrence occurred in all patients over 1–4 years
Farid *et al*. 2013[73]	9/109	Curative surgery with R0 resection	Adjuvant imatinib	None	Relapse 67% MS 141 months
Pai *et al*. 2016[74]	13	Three patients underwent intersphincteric resection (33.3%). For remaining patients, APR was performed	Neoadjuvant imatinib and adjuvant imatinib	None	One patient developed distant metastasis and none of the patients developed local recurrence

Contd...

Supplementary Table 2: Contd...

References	Rectal GIST/ total, *n*	Surgery	Chemotherapy	Radiotherapy	Outcome
Zanwar *et al*. 2016[23]	26	Sphincter-sparing surgery/ intersphincteric resection. In patients not amenable for sphincter preservation, an abdominoperineal resection or a pelvic exenteration based on local extent of the tumor	Imatinib for large tumors (>5 cm) Adjuvant imatinib in patients with high-risk recurrence criteria	None	Median PFS 120 months in the whole cohort whereas median OS was not reached 4-year PFS was 81% and OS was 100% Median DFS in upfront surgery 70 months, neoadjuvant imatinib group 120 months ($P = 0.039$). One patient had died

GISTs: Gastrointestinal stromal tumors; DFS: Disease-free survival; APR: Abdominoperineal resection; MS: Median survival; OS: Overall survival; PFS: Progression free survival; NA: Not available; RFS: Relapse free survival; HAR: High anterior resection; SBRT: Stereotactic body radiation therapy; hypofractionation of ≥500 cGy per fraction utilizing image guidance for delivery.