

Case Report

Effectiveness of radiation therapy in GIST: A case report

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KEY WORDS

Gastrointestinal stromal tumor (GIST), radiation therapy, intensity modulated radiation therapy (IMRT), imatinib mesylate, mesenchymal tumor

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Introduction

Over the last decade, gastrointestinal stromal tumor (GIST) became the most commonly diagnosed mesenchymal tumor of the gastrointestinal tract (2,3). Population-based studies suggest an annual incidence of between 11 and 14.5 per million and a prevalence of 129 per million (8). The immunohistochemistry of GIST shows the presence of cell-surface antigen CD117 (KIT), which represents a defining characteristic of GIST (4-7). Immunostaining is essential to differentiate GISTs from other more rare mesenchymal tumors. Differential diagnosis includes leiomyosarcomas, leiomyomas and schwannomas (8). It is believed that GISTs arise from a neoplastic transformation of the intestinal pacemaker cells known as the interstitial cells of Cajal (ICC) (6,9).

Prior to 2002, the only available therapeutic option for patients with localized GISTs was surgical resection (10). Unfortunately, even when excised in negative surgical margins, the recurrence rate for lesions larger than 3 cm was found to be significant. Introduction of the first tyrosine kinase inhibitor, imatinib mesylate, has dramatically changed the management options available for GIST patients (11). The role of radiation therapy in the treatment of GISTs has not been documented (12). In the past, clinicians were reluctant to use radiation therapy due to

concerns over the dose received by normal tissues, mostly the potential gastrointestinal toxicity. As such, radiation therapy has been utilized rarely, mostly for palliation purposes (13).

In this report, we describe the successful use of intensity modulated radiation therapy to treat an individual with large intra-abdominal GIST lesions (Figure 1), which were deemed unresectable. An initial attempt at systemic treatment with imatinib was not tolerated by the patient and did not produce a significant response.

Case presentation

A 62 year-old African American male presented with complaints of lower abdominal pain for 3 months. He also had complaints of constipation, urinary frequency and weight loss for the same duration. Medical history was positive for hypertension and gallstones. His sister had an unknown malignancy. On physical examination, there was an ill-defined mass in the right lower abdomen. There was no lymphadenopathy or lower extremity edema. The rest of the physical examination was unremarkable. CT scan showed two huge, largely homogenous masses. The superior lesion measured 10.2 cm × 13.3 cm × 12.3 cm, located in the right upper quadrant, and the inferior mass was slightly larger, measuring 14.8 cm × 11.5 cm × 12.3 cm, and was located in the retroperitoneum (Figure. 1). Biopsy was performed. Histopathological examination revealed a gastrointestinal stromal tumor, epithelioid type, with high risk features (Figure 2). Patient was started on systemic therapy with imatinib mesylate (400 mg, po, qd) but developed fluid retention, protracted nausea and lower extremity edema on imatinib. Despite dose adjustments and drug holidays the imatinib was not tolerated, requiring discontinuation. Patient was referred for radiation therapy. Radiation therapy

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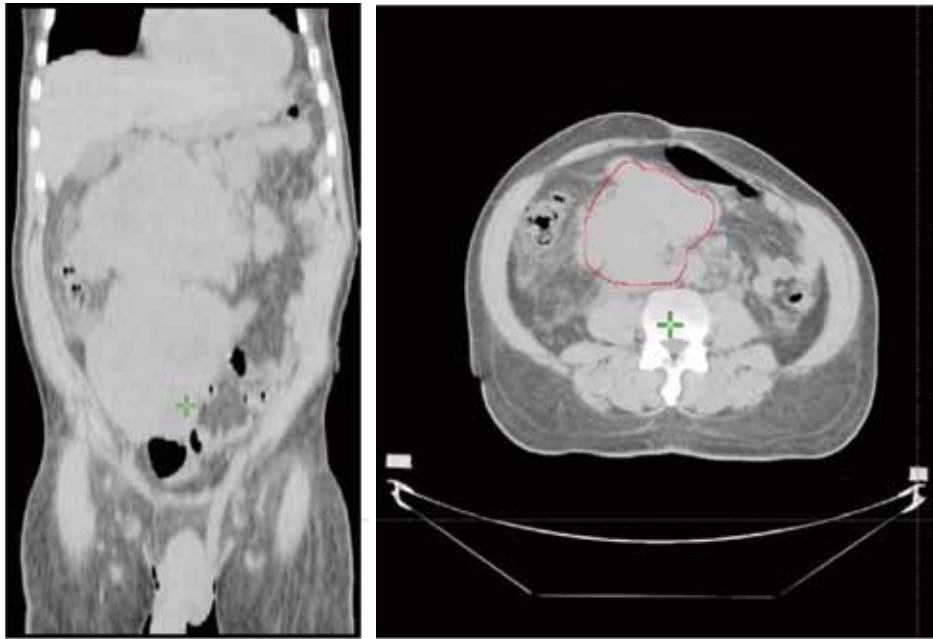


Figure 1. CT images of solid homogenous mass before radiation therapy (8/2/2010).

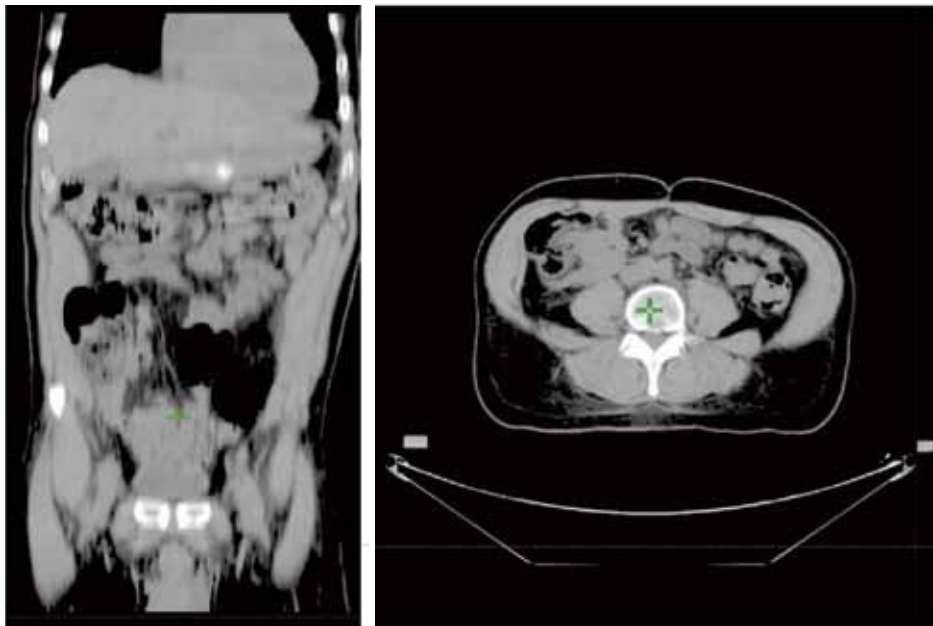


Figure 2. CT scan post radiation therapy (11/1/2010) showing a dramatically reduced solid mass with necrosis after treatment with 63.4 Gy.

was administered conformally using initially a pair of left anterior oblique (LAO)/right posterior oblique (RPO) field arrangement to 43.2 Gy in 27 fractions, followed by a cone-down setup with an IMRT technique to a total of 63.4 Gy. Despite of the high dose, the radiation therapy was well tolerated and relieved the patient's symptoms with a dramatic reduction in tumor size demonstrated by CT scan (Figure 1,2).

Discussion

Gastrointestinal stromal tumors (GIST) account for less than 1% of all gastrointestinal (GI) tumors (14,15). In 1983, Mazur and Clark introduced the term GIST to describe a distinctive subgroup of GI mesenchymal tumor, which had neither neurogenic nor smooth muscle origin (1,16). It is

believed that GISTs arise from a neoplastic transformation of the intestinal pacemaker cells known as the interstitial cells of Cajal (ICC) (9).

There is no strong predilection for either sex and these tumors can occur across a wide range of age groups (17). However, men are slightly more affected than women, and 75% of those diagnosed are over the age of 75 (18,19). So far, no link to environmental exposure, or relation with geographic location, ethnicity, or occupation has been established with incidence of GIST (20).

Morphologically, GISTs can appear as epithelioid, spindle cell, or a mixture of the two (21,22). The major histologic marker CD117, an epitope for the extracellular domain of KIT transmembrane receptor tyrosine kinase, stains positively in 95% of GISTs with a characteristic dot-like cytoplasmic pattern (23). Other important histological markers include CD34 (60-70%), ACAT (30-40%), DES (1-2%) and keratin (1-2%) (24).

GISTs show a diverse clinical presentation, with the most common symptoms being the presence of a mass or bleeding (2). The distribution of primary GISTs also varies throughout the gastrointestinal tract, with approximately 60-65% arising in the stomach, 20-25% in the small intestine, 5-10% in the colon or rectum and 5% in the esophagus (9,19).

The current treatment of choice for localized disease is surgical removal of the tumor with careful attention not to rupture the pseudocapsule. Unfortunately, less than 50% of patients have localized disease at diagnosis (18), and even when a curative resection is performed with clear margins the recurrence rate is approximately 50% (25). This recurrence rate can reach as high as 90% for large tumors with high mitotic rates.

In cases where the disease is extensive or the patient is not a surgical candidate, the choice of therapy is molecularly targeted chemotherapy with imatinib. Prior to the use of imatinib, chemotherapy results were dismal with reported success rates of 0-5% (18). The introduction of imatinib as a chemotherapeutic agent has greatly improved the treatment for non surgical candidates, with initial success rates of 70-90% (26). However, patients that do show an initial response are not cured and must stay on the drug indefinitely to prevent relapse (27). Furthermore, most patients eventually relapse and die of the disease (28,29).

Sunitinib malate, an oral agent inhibiting-multiple-tyrosine-kinases including KIT, PDGFR α as well as vascular endothelial growth factor receptor is recommended as second line of treatment for patients who experience disease progression while on imatinib treatment or who have life-threatening side effects. Although 20% of patients treated with Sunitinib have been stable for 2 or more years, age

above 60 years, poor performance status, pretreatment with higher doses of imatinib and primary resistance to imatinib are predictors for poor response to treatment. Additionally, thrombocytopenia and hand-foot syndrome, frequently leads to poor tolerability (31).

The role of radiation therapy in the treatment of GISTs has not been documented and, in our opinion, it may be underutilized clinically. As stated previously, concerns over the potential side effects have led to a limited role of radiation therapy, mainly for palliative purposes, or in cases of intraperitoneal hemorrhage (2). It has been suggested that radiation may also sensitize GIST tumors to imatinib, although this has not been definitively established (30). The current radiation therapy techniques facilitate the administration of very high and effective doses to the target areas, while protecting efficiently surrounding vital structures. These new radiation technologies have not been explored in GIST tumors and deserve more study.

Conclusions

The enthusiasm for the targeted therapies in GIST tumors marginalized the use of the more conventional radiation therapy for GIST tumors. In our case, the judicious use of modern techniques of radiation produced an impressive response in a case of large intra-abdominal GIST masses, while being very well tolerated. It is too early to determine the length of response in this patient, yet similar techniques of radiation may prove even more efficient in earlier cases. We recommend, therefore, using radiation therapy more often not only for palliation purposes, but also for definitive treatment, with or without imatinib or sunitinib.

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