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Stereotactic radiotherapy produces a durable response in a peri-rectal GIST

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Stereotactic radiotherapy produces a durable response in a peri-rectal GIST

Running Head: Long term control of SBRT in high-risk GIST

Case Report: Stereotactic radiotherapy produces a durable response in a peri-rectal GIST.

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Abstract

Background: Gastrointestinal stroma tumours (GISTs) are rare mesenchymal tumours originating from the gastrointestinal tract, which are classically managed with surgical resection and systemic therapy. GISTs are traditionally considered radioresistant, however there is mounting evidence of radiotherapy's utility within this tumour pathology.

Case presentation: Here we present a 60-year-old gentleman with locally advanced and metastatic peri-rectal GIST who was referred for consideration of stereotactic body radiotherapy (SBRT) to oligoprogressive peri-rectal masses whilst receiving second line systemic therapy (Sunitinib). He received SBRT 50 Gy in 5 fractions over a two-week period and tolerated treatment well. Thirteen months post-treatment, CT and PET CT imaging reveals ongoing reduction of the peri-rectal GIST lesion, with a favourable metabolic response. The patient remains active and working.

Conclusion: Radiotherapy is becoming a valuable alternative in GIST management for patients who are unable to tolerate or develop resistance to systemic therapy or have unresectable disease. This case further supports the use of SBRT in control of GIST, which has the potential to provide long term control.

Key words

Gastrointestinal stromal tumour (GIST), Stereotactic body radiotherapy (SBRT), Rectum

Introduction:

Gastrointestinal stromal tumours (GISTs) are mesenchymal neoplasms representing just 1-2% of primary gastrointestinal (GI) malignancies. The rectum is an uncommon primary site representing 5% of all GISTs[1]. In view of the targetable c-kit mutation found in the majority of tumours, the mainstay

of systemic therapy is tyrosine kinase inhibitors (TKIs). Although good, durable responses to TKI therapy are common, most patients subsequently develop resistance. Non-surgical procedures rather than commencement of a subsequent line of systemic therapy can be considered in cases of focal progression[2].

Palliative radiotherapy is advocated for selected patients[2], although there has historically been concern that GISTs are frequently radioresistant. Additionally, the deliverable dose is often limited by the surrounding organs at risk[3].

More recently however, conventional palliative radiotherapy has been demonstrated to provide high rates of symptomatic benefit and durable control amongst some patients[4,5].

Stereotactic body radiotherapy (SBRT) offers the potential to deliver ablative doses of radiotherapy whilst minimising the dose to surrounding organs at risk[6] and therefore may improve responses of GISTs to radiotherapy. Partial responses to Cyberknife stereotactic radiotherapy for soft tissue metastasis[7] and SBRT to bone metastasis[8] have been described.

Case description:

A 60-year-old gentleman with locally advanced and metastatic peri-rectal GIST was referred for consideration of SBRT to oligoprogressive peri-rectal masses whilst receiving second line systemic therapy (Sunitinib).

The patient initially presented in early 2016, with rectal bleeding, increasing pelvic pain and a palpable pelvic mass. Digital rectal examination revealed a posterior extrinsic mass. Investigations demonstrated a tumour posterior to the rectum, without evidence of metastatic disease on CT scan. Colonoscopy revealed no intraluminal lesion and normal

overlying mucosa. He proceeded to transperineal resection of a 10 cm tumour; histopathology confirmed a GIST with high mitotic index and positive surgical margins.

His past medical history was otherwise notable for hypertension and arrhythmia, for which he has an implantable cardioverter defibrillator. At the time of diagnosis, he was otherwise fit and working as an engineer.

A planned three-year course of adjuvant Imatinib was commenced in May 2016, unfortunately, commencement was delayed due to pre-existing gastritis and the patient ceased treatment after one month due to symptoms of reflux. A restaging CT in November 2017 demonstrated both local pelvic recurrence as well as hepatic metastases. He re-commenced Imatinib and had an excellent response to treatment, with regression of the hepatic lesions. He subsequently tolerated Imatinib well with only mild side effects of periorbital oedema. In March 2020, Imatinib dose was increased due to local progression. In view of further progression, systemic therapy was switched to Sunitinib in late April 2020.

In September 2020, the primary tumour had regrown to approximately 8cm (Fig 1, A-C). It was anticipated that further surgical resection would not achieve negative margins and, debulking was also felt not to be appropriate. He was referred for consideration of radiotherapy. Other metastatic lesions (liver) were stable with no-avidity on FDG PET imaging. The only reported symptoms were rectal and perineal pain as well as pain on defecation.

Stereotactic radiotherapy was planned for a dose of 50Gy in 5 fractions to the peri-rectal GIST.

Imaging simulation was undertaken through positioning the patient supine with an individualized BodyFix (Elekta) indexed to treatment couch, with a comfortably full bladder (~250-350mL, obtained through a drinking protocol of 3x 200ml water cups/30mins prior to

treatment) and empty rectum (<3cm diameter). Enemas are used if the rectum is greater than 3cm but were not required in this patient for simulation or treatment. The simulation CT was performed on Siemens Somatom, Definition 64 (Munich, Germany) with 1mm slice thickness. Scanner specifications: - 78cm Gantry aperture; - OIL/AIR, OIL/WATER tube cooling; - 100-80kW output; - Range: 28-665mA (optional 800); - Max load capacity 227 (299 Optional); - Reconstruction matrices 512x512. The planning MRI was performed on a 1.5 T Siemens Magneto Avanto Syngo MR B17® (Siemens Healthcare, Erlangen, Germany). This study's MRI sequence was a high-resolution T2-weighted scan with the following MRI parameters: T2 turbo-spin echo (TSE) with TR: 1250ms, TE: 185ms, with a voxel size of 1mm.

The simulation CT and MRI and diagnostic PET-CT was transferred to MIM Maestro version 6.6.13 (Cleveland OH, USA) (MIM) for radiotherapy contouring. The peri-rectal tumour as visualised on diagnostic CT, PET-CT and MRI was delineated as gross tumour volume (GTV). Clinical target volume (CTV) was defined as equal to the GTV. Planning target volume (PTV) was created by adding isotropic 5 mm margin to GTV, according to institutional policy.

Radiotherapy planning was performed in Monaco (v5.11.03, Elekta AB, Sweden). The PTV coverage aimed to achieve a dose of 50Gy [total dose (TD)] to 95% of the volume (D95) and a 47.5Gy (p5% TD) to 99% of the volume (D99). The mean dose to the GTV was 55Gy with a maximum dose of 70Gy (reported Max 0.035cc 70.141Gy). However, the PTV coverage was compromised to achieve the organs at risks constraints with the D95 of 27Gy, D99 of 24Gy and a GTV minimum dose of 25Gy.

The organs at risk were constrained according to dose volume constraints, that were all achieved. The cauda equina (spinal canal), sciatic nerve and sacral plexus (including planning organ risk volumes PRVs) were constrained to a maximum dose (Dmax to 0.035cc) of 32Gy and the volume receiving 30Gy (V30) was constrained to 5cc. Large bowel/rectum (iRectum was created using

rectum positioning from multiple scans), bladder and femoral heads with PRVs were constrained to a maximum dose (Dmax to 0.035cc) of 38Gy. Volume constraints for large bowel/rectum, bladder and femoral heads were V25<20cc, V18.3<15cc and V30Gy<10cc. Ureters were constrained to a Dmax to 0.035cc of 50Gy. The patient was mocked on treatment machine pre-CT simulation with Cone-beam CT to confirm visualisation of target and OARs (Rectum).

The standard CBCT parameters consisted of 41cm diameter FOV, M20 (scan length:24cm), 120 kVp, 25 mA 40ms nominal per frame, 660 frames per scan (360 degrees rotation), 1mm voxel size, 2-3mm viewing slice resolution with an axial resolution of 512 x512. The patient was treated on an Elekta Versa HD Linac (Stockholm, Sweden), using VMAT SABR 6MV (Dose rate 400MU/m due to pacemaker) to a dose of 50Gy in 5 fractions over two weeks, utilising a Hexapod 6^{o} of freedom couch top. The departmental SABR verification protocol comprises 2 daily pre-treatment, online cone-beam CT (CBCT). 1 mid treatment online CBCT (where treatment time exceeds 10min) and 1 post treatment CBCT. Matching to bone in the treatment area translational and rotational corrections followed by a grey value mask match of the PTV +0.5cm only applying translational corrections from the soft tissue match. The initial pre-treatment CBCT shift was confirmed with a second CBCT. Zero tolerance for initial pre-treatment CBCT was applied, all following images to be within 0.2cm and 2 degrees. Otherwise, Zero tolerance applied then re-imaged to confirm shift/patient position.

Treatment was tolerated well although rectal/perineal pain increased during the final week of radiotherapy requiring commencement of Oxycodone. Sunitinib was paused during the SBRT course (for two weeks), due to the potential increased risk of bowel perforation.

Initial post-radiotherapy CT at 2 months demonstrated a slight reduction in size of the peri-rectal masses and no evidence of progressive disease elsewhere. At 7 months post-SBRT (August 2021), there was increasing central hypoenhancing areas likely due to central necrosis; a PET CT at this time point demonstrated decreased FDG avidity reflective of excellent metabolic response. Recent rectal

examination findings (March 2022) are also consistent with reduction in size compared with November 2020. The most recent CT and PET CT imaging in February 2022 demonstrate ongoing reduction of the bilateral peri rectal mass lesions (measuring approximately 63x40mm; previously 80x54mm in August 2021), with favourable metabolic response (Fig 1, A-E). A previously noted right mesorectal mass is no longer FDG-avid and has decreased in size. Nil evidence of hepatic or new FDG-avid disease are observable. He continues on Sunitinib and is tolerating this well without any specific toxicities. He is still active and working.

Discussion:

Historically, GIST has been considered relatively radioresistant to standard radiotherapy fractionation[9] due to exaggerated repair mechanisms, mainly from gain of function mutations in KIT or PDGFRα[10]. Given the potential for GIST tumours to recur or develop resistance to systemic therapy; radiotherapy is becoming increasingly recognised as a viable treatment option and recent evidence suggests that SABR may produce better local control[8]. Additionally, there has been clinical concern about the adverse effects of radiation on the abdominal organs, however a systematic review by Zhang *et al.* (2022) report that radiotherapy combined with TKI's should be considered, especially for GISTs at high risk of local recurrence, where surgery is often damaging, specifically for rectal GISTs[9], as occurred with our patient. A report by Miettinen and Lasota (2016) found that distant metastases occurred in more than 50% of patients with intestinal GISTs who had > 5 mitoses per 50 high power fields, or with a tumour size larger than 5 cm[11]. Given such metastatic recurrence risk, there is a need to consider alternative or adjunctive treatment options that could help reduce metastases or that are valuable in the recurrent context[11]. A study by Gatto *et al.* (2017) report a case of a 44-year-old gentleman with a gastric GIST with multiple liver metastases who failed Imatinib and Sunitinib therapy. He underwent a partial gastrectomy and right hepatectomy, consequently developing a 34mm right pararenal GIST (high mitotic index) and was treated with cyberknife treatment (first at 45 Gy delivered in 5 sessions, with a subsequent second treatment of

40Gy in 4 sessions, after 60 days)[7]. The treatment was well-tolerated and patient experienced disease stabilisation for a time, however eventually developed a left supraclavicular mass (diameter 46 × 37 mm), which led to a sunitinib rechallenge combined with cyberknife treatment of the supraclavicular mass (32 Gy in 5 sessions). This led to local tumour control and prolonged symptomatic improvement.

This case is similar to our report, whereby the patient underwent initial resection of the GIST, and subsequently failed both Imatinib and Sunitinib therapy; his metastatic lesions had a high mitotic index. It is different to our case in that the patient underwent two SBRT regimen. The dose of the initial SBRT for each patient was relatively equivalent between patient's (50Gy in 5 for our patient, and 45Gy in 5 fractions for Gatto *et al.* patient[7]). Perhaps the degree of oligometastatic spread of the GIST was more extensive in the Gatto *et al.* patient, or that our patient experienced stability of his hepatic metastatic lesions with no avidity on FDG PET imaging, from Imatinib and subsequent Sunitinib therapy.

Yilmaz *et al.* (2020) report a case of a 31-year-old male who presented with a small intestinal GIST (low grade), underwent surgical resection and was commenced on Imatinib[8]. After two years, the patient subsequently developed a solitary, lytic right iliac bone metastasis (high grade mitoses) and was treated with Sunitinib and SABR (24 Gy in 3 fractions) The patient experienced a complete response in the right iliac bone and was still in remission at 16 months follow-up after SABR, without any acute or chronic side effects from SABR treatment[8]. This favourable response at a lower dose than our patient received is quite interesting. The serosal margins from the initial resection were positive, akin to our patient's margins, however no local recurrence was observed. Efficacy of Iimatinib and Sunitinib is both tumour location and genetically dependent, and combined use of TKI's with SBRT can afford increased radiosensitivity of tumours, which is known[9].

This case gives further impetus to a role for radiotherapy in the management of GIST patients with gross or microscopic residual disease post-surgery, or who have locally recurrent disease. SBRT can enable an ablative dose to be delivered to these tumours, which may provide a more significant and durable response than standard palliative regimes by possibly overcoming the radioresistance of GIST. In more common radiation resistant tumours, such as renal cell cancer, SABR has improved local control[12, 13], presumably because the large doses per fraction override repair mechanisms[14, 15]. In RCC it has been implied that fractional doses greater than 10Gy per fraction with a total dose EQD2>100Gy are important to achieve optimal control[16]. There is a wide variation in SABR dose and optimal dose fractionations in general have not been well established[12]. In this patient, 50Gy in 5 fractions over a two-week period was prescribed to optimise local control in a radioresistant tumour by achieving high doses in the GTV and maintaining a mean dose of 50Gy while respecting the dose constraints of adjacent organs risk. This report further illustrates that the use of SBRT with resistant TKIs can produce a solid, protracted objective response in patients. As radiotherapy is further appreciated in GIST management, the potential to achieve long-term survival with aggressive local therapy like SBRT, in patients who have relapsed, is becoming a reality.

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Fig 1. Axial and coronal CT and PET images of Rectal GIST, before and after SBRT. A-C: Peri-rectal GIST pre-SBRT. C-E: Axial and coronal CT and PET images demonstrating reduced peri-rectal GIST, performed 13 months post-SBRT.