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Published in:
Radiotherapy and Oncology

DOI:
10.1016/j.radonc.2015.07.025

2015

Radiotherapy and Oncology 116 (2015) 233–238

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Radiotherapy for GIST

Radiotherapy for GIST progressing during or after tyrosine kinase inhibitor therapy: A prospective study

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ARTICLE INFO

Article history:
Received 9 April 2015
Received in revised form 18 June 2015
Accepted 16 July 2015
Available online 27 July 2015

Keywords:
Gastrointestinal stromal tumor (GIST)
Radiotherapy
Imatinib
Sunitinib

ABSTRACT

Purpose: Gastrointestinal stromal tumor (GIST) has been considered radiation-resistant, and radiotherapy is recommended only for palliation of bone metastases in current treatment guidelines. No registered prospective trial has evaluated GIST responsiveness to radiotherapy.

Patients and methods: Patients with GIST progressing at intra-abdominal sites or the liver were entered to this prospective Phase II multicenter study (identifier NCT00515931). Metastases were treated with external beam radiotherapy using either conformal 3D planning or intensity modulated radiotherapy and conventional fractionation to a cumulative planning target volume dose of approximately 40 Gy. Systemic therapy was maintained unaltered during the study.

Results: Of the 25 patients entered, 19 were on concomitant tyrosine kinase inhibitor therapy, most often imatinib. Two (8%) patients achieved partial remission, 20 (80%) had stable target lesion size for $\geqslant$3 months after radiotherapy with a median duration of stabilization of 16 months, and 3 (12%) progressed. The median time to radiotherapy target lesion progression was 4-fold longer than the median time to GIST progression at any site (16 versus 4 months). Radiotherapy was generally well tolerated.

Conclusions: Responses to radiotherapy were infrequent, but most patients had durable stabilization of the target lesions. GIST patients with soft tissue metastases benefit frequently from radiotherapy.

Gastrointestinal stromal tumors (GIST) frequently give rise to liver and intra-abdominal metastases. Imatinib, an inhibitor of KIT, PDGFRA, and a few other kinases, is the standard first-line agent for metastatic GIST [1,2] with responses lasting for a few years, but acquired drug resistance is frequent. Sunitinib is approved for patients whose GIST is refractory to imatinib or who do not tolerate imatinib [3], and regorafenib for those whose disease does not respond to imatinib and sunitinib [4]. The median time to GIST progression on sunitinib and regorafenib is 6 and 5 months, respectively [3,4]. Most patients with advanced GIST will eventually receive palliative care.

Some retrospective data suggest that radiotherapy is not beneficial in the treatment of GIST [5], and GIST has been considered radiotherapy-resistant or minimally responsive [6–9]. Current treatment guidelines do not discuss radiotherapy as a therapeutic option [1], or consider it only for palliation of rare bone metastases [2]. However, results from a few case reports (reviewed in [10]) and a retrospective series with 15 patients [11] suggest that advanced GIST is not uniformly radioresistant and that selected patients may benefit from radiotherapy.

To our knowledge, no prospective study has investigated palliative radiotherapy as the treatment of GIST. We report here the first prospective trial addressing this patient population.

Patients and methods

Study design

The study was a non-randomized, prospective multicenter trial. Patients were registered centrally and reviewed for eligibility prior to radiotherapy initiation. The primary endpoint was target lesion response to radiotherapy. Secondary objectives included time to progression (TTP) of the irradiated lesions, TTP of GIST at any site, survival, and adverse effects associated with radiotherapy.

Patients

Eligible patients had histologically verified inoperable GIST, either locally advanced or metastatic disease. Tumor immunostaining for KIT was done in all cases as part of the diagnostic

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http://dx.doi.org/10.1016/j.radonc.2015.07.025
0167-8140/

procedures. We required that tyrosine kinase inhibitor treatment had been administered before study entry or that the patient did not tolerate tyrosine kinase inhibitors, ⩾1 GIST lesions were progressing during or after tyrosine kinase inhibitor therapy, and that the target lesions selected for radiotherapy were measurable. We excluded patients with World Health Organization (WHO) performance status 4, pregnant women, and cases where radiotherapy was not considered feasible due to infection, restlessness, or other reasons, or if the planning target volume (PTV) defined by the 90% isodose [12] was >3000 cm^3.

The study protocol (NCT00515931, www.ClinicalTrials.gov) was approved by an Ethics Committee. Each patient provided written informed consent prior to study entry.

Procedures

External photon beam therapy was given with a linear accelerator. Radiotherapy was administered as conformal 3-dimensional (3D) radiotherapy or intensity-modulated radiotherapy (IMRT), and planning was based on computerized tomography (CT). Use of ⩾2 portals was mandated. The clinical target volume (CTV) encompassed the gross tumor plus a margin of approximately 1 cm. The planning target volume (PTV) encompassed the CTV plus the margin required by target movement and dose fall-off, typically the CTV plus 0.5–1.0 cm. Radiotherapy was given in 1.8–2.0 Gy daily fractions, 5 fractions weekly, to a cumulative PTV dose of 30–40 Gy [12].

The World Health Organization (WHO) performance status, symptoms, weight, and blood cell counts and biochemistry were assessed and CT of the abdomen was done ⩽2 weeks that preceded initiation of radiotherapy, and these investigations were repeated 6 and 12 weeks, and 6 months after radiotherapy completion. The CT scans were reviewed centrally for tumor response by a professional radiologist. Adverse effects were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.3.0, and were captured on structured forms at baseline and at the scheduled follow-up visits.

Tyrosine kinase inhibitor therapy that was ongoing at study entry was allowed to continue during the study, but we required the dosing to be kept unaltered to allow reliable radiotherapy response evaluation. Palliative medication and medication indicated for other diseases but GIST were allowed.

Statistical analysis

Treatment response was defined either as complete response (CR) or partial response (PR) by RECIST1.0 or as stabilized disease (SD) for >12 weeks. Gehan 2-stage procedure was followed in sample size estimation. Chance of rejecting treatment response of 20% was considered to be <0.05 (1-β 0.95) when 14 patients were entered to the trial in the first phase. If ⩾3 (21%) of the 14 patients benefitted from radiotherapy, 11 further patients were entered to reach a maximum of 25 patients.

Response duration was calculated from the date of first occurrence of response to the date of disease progression, death, or the date of last follow-up. The duration of SD was calculated with the Kaplan–Meier life-table method from the first date of radiotherapy to the date of target lesion progression or death, whichever occurred first, censoring patients alive without target lesion progression on the date of last follow-up. Time to GIST progression was computed from the date of radiotherapy initiation to the date of first GIST progression at any site or death from any cause when death preceded GIST progression, censoring patients who were alive without progression on the last date of follow-up. Time to radiotherapy target lesion progression was computed from the date of radiotherapy initiation to the date of first GIST progression in the PTV or to death. Overall survival was calculated from the date of radiotherapy initiation to the date of death censoring patients alive.

The safety population included all registered patients. Continuous distributions between groups were compared with the Mann–Whitney *U*-test. Lesion densities at baseline and after radiotherapy were compared with the Wilcoxon signed rank test. Survival between groups was compared using the log-rank test. The *P* values are 2-sided. The data were analyzed using a Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Twenty-five patients were registered through January 29, 2008 and February 2, 2014 from 3 study sites (Table 1). All patients had received imatinib prior to radiotherapy, and 15 (60%) also sunitinib. Ten (40%) patients had been treated with ⩾3 tyrosine kinase inhibitors before radiotherapy. None had received prior radiotherapy for GIST, but 13 (52%) had surgery to remove metastases.

The patients had metastatic GIST. The sites of the lesions are provided in Table 1. Twenty-one (84%) of the 25 patients had an intra-abdominal tumor and 4 (16%) liver metastases as the target lesions. Sixteen (64%) patients had 1 target lesion, 4 (16%) patients had two, and 5 (20%) 3–5 target lesions. The median largest target tumor diameter was 6.8 cm (range, from 2.4 to 14.5 cm). The median cumulative PTV dose was 39.6 Gy (range, from 30.0 to 40.0 Gy), which was achieved in a median of 28 days using conformal 3D planning (18 patients) or IMRT (7 patients). Six (24%) patients did not receive tyrosine kinase inhibitors during radiotherapy, whereas 19 (76%) were maintained on the prior systemic therapy on which the radiotherapy target lesions had progressed (11 [44%] continued to receive imatinib, 4 [16%] sunitinib, 2 [8%] nilotinib, 1 [4%] regorafenib, and 1 [4%] had a combination of sorafenib and everolimus).

The median follow-up time was 19 months (range, from 2 to 74 months), and patients alive at the time of data collection closure (September 2014, $n = 7$) were followed up for a median of 7 months (range, from 6 to 41 months). Twenty (80%) had GIST progression during the follow-up, and 18 (72%) died.

Two (8%) patients achieved PR as the best response based on central assessment, 20 (80%) had SD, and 3 (12%) progressed within 3 months from radiotherapy. The objective response rate (CR or PR) was thus 8% (95% CI, from 0% to 19%), and the clinical benefit rate (CR, PR, or SD) 88% (95% CI, from 75% to 100%). The per cent longest diameter changes of the target lesions measured 3 months after radiotherapy as compared with the baseline diameters are provided in Fig. 1.

One patient with PR had the target lesion excised surgically 3 months after starting radiotherapy, and the response of the second patient with PR lasted for 10 months. The estimated median duration for the PTV lesion stabilization in the subset of patients who had SD as their best response to radiotherapy ($n = 20$) was 16 months (8 stabilizations were ongoing at the time of the analysis 6 to 45 months after starting radiotherapy).

The median time to first GIST progression at any site was 4 months (95% CI, form 1 to 7 months). The irradiated lesions progressed in 14 (58%) patients during the follow-up. The estimated median time to target lesion progression was 16 months (95% CI, from 5 to 27 months). Since GIST progressed in 14 (58%) out of the 24 evaluable patients outside of the PTV before progressing within the PTV, this frequently led to a change in systemic therapy. As this confounds radiotherapy response duration evaluation, we calculated also the time from radiotherapy initiation to either GIST progression within the PTV or to a change in systemic

Table 1
Characteristics of the patients and the tumors.

Characteristic	Median (range)	Number (%)
Age (years)	61.4 (19.7–86.5)	
Gender		
Male		17 (68)
Female		8 (32)
WHO performance status		
0		9 (36)
1		12 (48)
2		4 (16)
Primary tumor site		
Stomach		6 (24)
Small intestine		13 (52)
Colon/rectum		3 (12)
Other		3 (12)
Primary tumor mitotic count (per 50 HPFs)	24 (2–250)	
Primary tumor mutation		
KIT exon 11		10 (40)
KIT exon 17		2 (8)
KIT exon 9		2 (8)
PDGFRA exon 12		1 (4)
Wild type for *KIT*/*PDGFRA*		6 (25)
Not available		4 (16)
Adjuvant imatinib		
Yes		5 (20)
No		20 (80)
Time from GIST diagnosis to detection of metastases (years)	0.06 (0–8.1)	
Metastatic sites[a]		
Liver		10 (40)
Intra-abdominal		19 (76)
Soft tissue		2 (8)
Bone		1 (4)
First-line agent for metastatic disease		
Imatinib		23 (92)
Sunitinib		2 (8)
Highest dose of imatinib administered		
400 mg/day		9 (36)
500–1000 mg/day		16 (64)
No. of systemic therapies prior to study entry		
1		7 (28)
2		8 (32)
3–5		10 (40)
Systemic agents given prior to radiotherapy[b]		
Imatinib		25 (100)
Sunitinib		15 (60)
Nilotinib		8 (32)
Sorafenib		8 (32)
Vatalanib		2 (8)
Regorafenib		1 (4)
Everolimus		1 (4)
Prior palliative surgery for metastases		
Yes		13 (52)
No		12 (48)
Time from GIST diagnosis to start of radiotherapy (years)	5.3 (0.8–26.4)	
Time from detection of metastases to radiotherapy (years)	3.5 (0.6–26.4)	

Abbreviations: GIST = gastrointestinal stromal tumor; HPF = high power field of the microscope; *PDGFRA* = platelet-derived growth factor alpha gene; WHO = the World Health Organization.
[a] One patient may have ⩾1 metastatic sites.
[b] One patient may have received ⩾1 systemic agents.

therapy, whichever occurred first, and censored patients who had no PTV progression on the date of a change in systemic therapy ($n = 6$). The estimated median time to target lesion progression

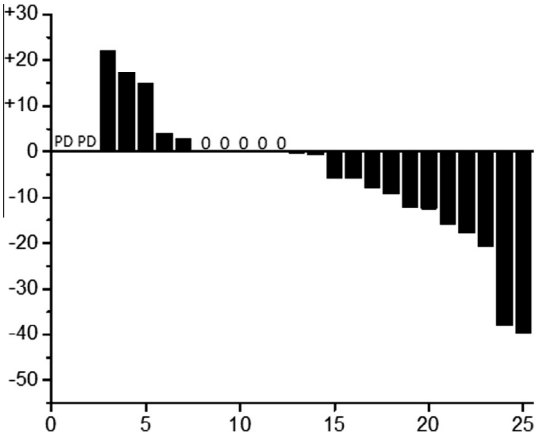

Fig. 1. A water-fall plot showing the changes in the longest target lesion diameters. The per cents refer to the ratio of the diameters measured centrally from a CT scan obtained 3 months after radiotherapy to the baseline diameter. Two patients with progressive disease (PD) did not have a CT taken 3 months after radiotherapy available; 5 tumors did not change in size.

or to a change in systemic therapy was 12 months (95% CI, from 1 to 22 months). The median overall survival time was 19 months (Fig. 2).

In the subset of patients with wild type GIST ($n = 6$) 2 patients achieved PR, 2 had SD, and 2 progressed, and their median time to target lesion progression was 11 months, which did not differ significantly from the rest of the patients ($P = 0.260$). Of the 6 patients who were not on tyrosine kinase inhibitor therapy during radiotherapy 1 achieved PR and 5 had SD, and their median time to target lesion progression was longer as compared with the 19 patients who received tyrosine kinase inhibitor therapy concomitantly with radiotherapy (23 versus 11 months; $P = 0.014$). One of the 4 patients with a liver lesion as the target achieved PR, and 3 had SD as their best response.

The effect of radiotherapy on target lesion density was studied as an exploratory analysis in 16 patients with a total of 25 evaluable target lesions (9 patients were excluded from the analysis; 6 did not receive a contrast agent prior to each CT scan, and 3 had PD prior to 3 months of follow-up). The target lesions were less dense 3 months after starting radiotherapy as compared with the baseline density (median, 36.1 versus 44.1 Hounsfield units [HU], respectively, $P = 0.017$).

None of the patients discontinued radiotherapy prematurely. Transient diarrhea was the most frequent adverse event recorded, and occurred in 13 (52%) of the 25 patients, followed by pain (44%), nausea (36%), and fatigue (32%, Table 2). Most patients (84%) had anemia. Adverse events were usually mild to moderate (grade 1 or 2), and only few patients had severe (grade 3) toxicity. One patient treated with IMRT for a 7.6 cm progressive liver metastasis to a cumulative dose of 39.6 Gy with 1.8 Gy daily fractions and who was on sorafenib 400 mg/day developed grade 4 biliary tract necrosis. No weight loss occurred between study entry and the first follow-up visit performed 6 weeks after completion of radiotherapy (median weight, 69.5 kg and 73.0 kg, respectively, $P = 0.167$).

Discussion

Only 2 patients achieved PR, which could be in keeping with the contention that GISTs are radiation-resistant, but as many as 20 of the remaining 23 patients had durable stabilization of the target lesion size. Considering that the median time to GIST progression at any site was only 4 months and the median survival time 19 months, the median time to radiotherapy target lesion

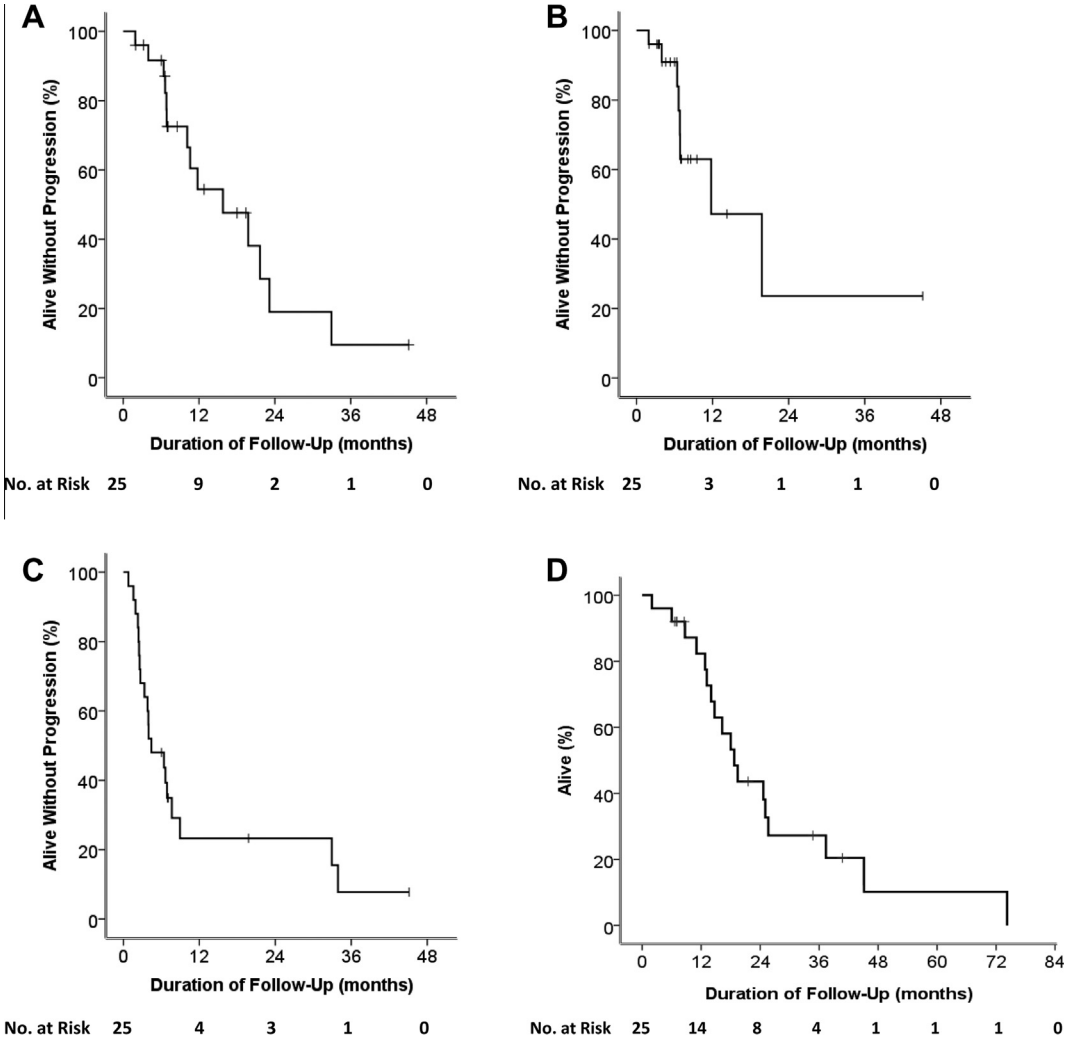

Fig. 2. Kaplan–Meier estimates of survival. (A) The time to radiotherapy target lesion progression; (B) time to target lesion progression or to a change in systemic therapy (whichever occurred first); (C) time to first GIST progression at any site; (D) overall survival. Patients censored are indicated with a bar.

progression of 16 months is long, since the target lesions were controlled for most of the remaining life-time of the patients. The patient population was typical of advanced GIST, except that 6 (24%) patients had wild-type GIST and 2 (8%) *KIT* exon 17 mutation. These mutational subgroups may have been enriched in the study population due to their limited responsiveness to tyrosine kinase inhibitors [13].

Estimation of response duration to local treatments may be confounded by systemic treatments even in heavily pretreated patient populations. Therefore, we performed a survival analysis where patients without progression within the PTV but progressing elsewhere and having systemic therapy changed were censored on the date of the therapy change. This produced a conservative estimate for the radiotherapy-related duration of SD, but the estimate was still relatively long with a median of 12 months. The responses we report are also conservative and for radiotherapy alone. One patient whose 10.8 cm metastasis decreased 18% in size following radiotherapy qualifying for SD, but disappeared after subsequent change in systemic therapy was thus reported as SD, and not CR.

Imatinib enhances sensitivity to radiotherapy in selected cell lines derived from various types of human cancer [14]. Most of the patients received tyrosine kinase inhibitors during radiotherapy, frequently imatinib, and, therefore, the efficacy achieved could result rather from the combined effects of radiotherapy and tyrosine kinase inhibitors, and might be less with radiation alone. Our findings might not support this hypothesis. The median time to target lesion progression was longer in the subset of patients who were treated with radiotherapy alone without concomitant tyrosine kinase inhibitors as compared to patients who were on maintained tyrosine kinase inhibitors during radiation, but this exploratory analysis was based on small patient numbers.

Radiotherapy was usually well tolerated. Pain of any grade was recorded in 11 (44%) patients during or after radiotherapy, but 16 (64%) patients had pain at study entry suggesting that much of the pain recorded was unrelated to radiotherapy. In contrast, diarrhea, nausea and fatigue were recorded in 13 (52%), 9 (36%), and 8 (32%) patients during or after radiotherapy but infrequently prior to radiotherapy (2 patients had fatigue, 1 diarrhea, and 1 nausea at study entry), suggesting that most of these adverse events were caused by radiotherapy. Anemia was frequently recorded, but this was more likely related to advanced GIST and tyrosine kinase inhibitor therapy than to radiotherapy.

One patient developed biliary tract necrosis, which was the only grade 4 adverse event observed. Tyrosine kinase inhibitors that inhibit the VEGF receptors may be associated with radiotherapy

Table 2
Adverse events registered.*

Adverse event registered in two or more patients	Maximum grade of severity registered			
	None N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)
Diarrhea	12 (48)	10 (40)	1 (4)	2 (8)
Pain	14 (56)	5 (20)	3 (12)	3 (12)
Nausea	16 (64)	8 (32)	1 (4)	0 (0)
Fatigue	17 (68)	5 (20)	1 (4)	2 (8)
Vomiting	19 (76)	5 (20)	1 (4)	0 (0)
Hemorrhage	21 (84)	2 (8)	1 (4)	1 (4)
Dyspepsia/heartburn	21 (84)	4 (16)	0 (0)	0 (0)
Constipation	23 (92)	2 (8)	0 (0)	0 (0)
Radiation dermatitis	23 (93)	2 (8)	0 (0)	0 (0)
Blood cell counts & blood biochemistry				
Anemia	4 (16)	12 (48)	7 (28)	2 (8)
Leukopenia	18 (72)	4 (16)	3 (12)	0 (0)
Thrombocytopenia	20 (80)	4 (16)	0 (0)	1 (4)
ALT increase	22 (88)	2 (8)	1 (4)	0 (0)
Alkaline phosphatase increase	15 (60)	9 (36)	1 (4)	0 (0)
Creatinine increase	13 (52)	9 (36)	3 (12)	0 (0)

Abbreviations: ALT = alanine aminotransferase.
* One grade 4 adverse event was recorded (biliary tract necrosis); no grade 5 (lethal) adverse events occurred.

recall reactions [15] and bleeding [16] at the irradiated sites, but a few Phase I and II trials suggest that concomitant administration of sunitinib and radiotherapy is safe [17,18]. In a recent Phase II study where sorafenib was administered both concomitantly and after radiotherapy for advanced hepatocellular carcinoma, 35% of the 40 patients treated developed $\geqslant$2 grade hepatotoxicity, and 15% had $\geqslant$3 grade hepatotoxicity, of which 3 incidents were fatal [19]. These findings suggest that tyrosine kinase inhibitors that inhibit the VEGF receptors are best used cautiously in patients irradiated for hepatic lesions.

We did not collect data about the quality of life, which is a limitation. The study accrual time was relatively long, possibly reflecting efficacy of systemic treatments and the undefined role of radiotherapy for GIST during the study. In our experience, progression of only one or a few metastases during tyrosine kinase inhibitors therapy is not uncommon in GIST.

Conventional fractionation and a modest cumulative dose were selected to be studied in this palliative setting, but further studies investigating other fractionation schemes and larger fraction sizes are warranted. In a recent retrospective series 6 (35%) of the 15 patients with GIST metastases usually treated with ten 3 Gy fractions with or without concomitant tyrosine kinase inhibitor therapy responded to treatment [11]. Selective internal radiotherapy with ^{90}Y microspheres has been found effective in anecdotal cases [13], and warrants further evaluation.

In sum, the results suggest that GIST metastases are moderately radiosensitive, and frequently stabilize for several months with radiotherapy. Radiotherapy appears to be a well-tolerated means to palliate patients who have advanced GIST progressing at one or a few sites.

Conflict of interest statement

Dr. Joensuu has received research funding from Novartis and Bayer AG; Dr. Eriksson has acted as a consultant to Isofol Medical AB and Bayer, has received honoraria from Novartis and Bayer, and other remuneration from GlaxoSmithKline and Swedish Orphan; Dr. Montemurro has received honoraria from Bayer and other remuneration from Bayer and Merck.

Acknowledgements

The study was supported by Louise and Henrik Kuningas Foundation, Cancer Society of Finland, Academy of Finland, Sigrid Juselius Foundation, Research Funds of the Helsinki University Central Hospital, and Jane and Aatos Erkko Foundation.

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