



Low-dose splenic irradiation is an alternative therapy for symptomatic splenomegaly in patients with myelofibrosis

Ming-Shan Huang¹ · Yu-Hsuan Chen^{1,2} · Chun-Wei Wang^{1,2} · Ming Yao³ · Sung-Hsin Kuo^{1,2,4,5} 

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Dear Editor,

Splenomegaly resulting from extramedullary hematopoiesis or lymphoid cell infiltration often results in abdominal pain, disturbances in breathing and daily activity, and early satiety in patients with hematological diseases of various origins [1, 2]. Because of splenic sequestrations, massive splenomegaly causes the hematologic changes such as anemia, thrombocytopenia, or leukopenia [1, 3]. Surgical splenectomy was once proposed for patients with symptomatic splenomegaly [4]. However, splenectomy may increase perioperative mortality or risk of opportunistic infection and thus is not considered a treatment choice for patients with poor medical conditions and comorbidities [4, 5].

In contrast to surgical splenectomy, splenic irradiation is a non-invasive treatment modality for palliative relief of symptoms of splenomegaly in patients with hematological diseases [6, 7]. Considering that extramedullary hematopoiesis from myeloid fibrosis or infiltration of leukemia cells or lymphoid cells is comparatively radiosensitive, different radiation doses of 0.3–16 Gy with fraction size ranging from 0.1 to 2 Gy have

been reported for the treatment of symptomatic splenomegaly in patients with hematologic diseases [7–10]. However, a few cohort series investigating the dose, fraction, and technique of splenic irradiation have been reported in patients with hematologic diseases accompanied by splenomegaly.

Between June 2004 and December 2016, 19 patients who received splenic irradiation for symptomatic splenomegaly (including palpable splenomegaly with gastrointestinal compression symptoms or progressive thrombocytopenia requiring platelet transfusion) of myelofibrosis were included in this study. The diagnosis of myelofibrosis was mainly based on the hematologic, morphologic, and cytogenetic manifestations in peripheral blood and marrow cells according to the World Health Organization classification of myeloid neoplasms [11]. Toxicities resulting from splenic irradiation were assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) scale version 4.0 [12].

The radiotherapy for splenomegaly was delivered using a photon beam with an energy of 6 MV or higher. An example of the beam arrangement and treatment field of the forward field-in-field intensity-modulated radiotherapy technique (IMRT) for reducing the inhomogeneity of the radiotherapy dose to the whole spleen is illustrated in Fig. 1a and in Supplementary Figure 1. The splenic irradiation was delivered to all patients twice a week, and radiotherapy was discontinued if symptoms were alleviated according to the clinical judgment of the physicians. The 9 men and 10 women who received splenic irradiation in this study had a median age of 59.3 (range, 3–72) years. Of these 19 patients, 11 patients received the 3D conformal radiotherapy and 8 patients received the forward field-in-field IMRT (Supplementary Table 1). The prescribed radiation dose ranged from 2 to 8 Gy with 0.5 to 1 Gy per fraction, 2 fractions per week, with a median total dose of 4 Gy and a median fraction size of 1 Gy (Supplementary Table 1).

After splenic irradiation, 18 (94.7%) of 19 patients had a shrinkage of splenic size of more than two finger breadths based on physical examination, indicating that splenic

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✉ Sung-Hsin Kuo
shkuo101@ntu.edu.tw

¹ Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan S Rd, Taipei, Taiwan

² Cancer Research Center, College of Medicine, National Taiwan University, Taipei, Taiwan

³ Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

⁴ Graduate Institute of Oncology, College of Medicine, National Taiwan University, Taipei, Taiwan

⁵ National Taiwan University Cancer Center, College of Medicine, National Taiwan University, Taipei, Taiwan

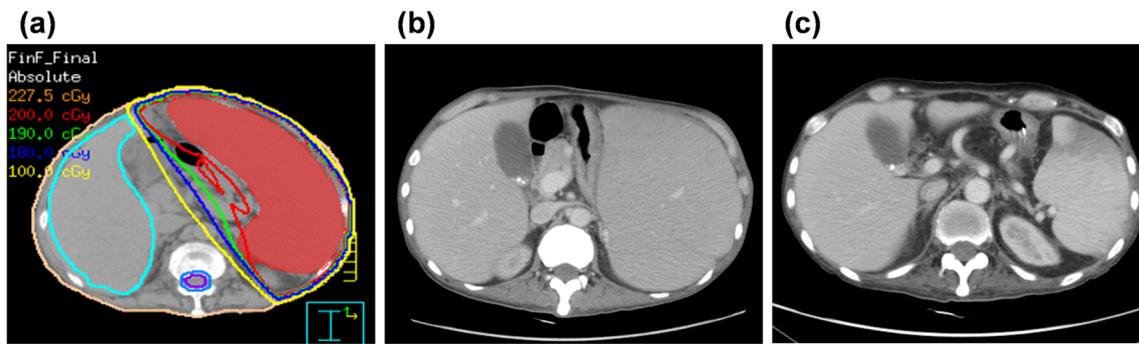


Fig. 1 The radiation field and the images of patients with myelofibrosis had splenomegaly accompanied by abdominal pain and discomfort. **a** An example of isodose curve of splenic irradiation for a patient with myelofibrosis (whole spleen was contoured and beam angles were designed to avoid scattered dose to adjacent normal tissues) is shown

below in an axial view. **b** A computed tomography image showed splenomegaly of the patient with myelofibrosis before splenic irradiation. **c** A computed tomography image showed significant improvement of splenic size of the same patient 6 months after splenic irradiation with a total of 4 Gy in four fractions twice a week

irradiation resulted in splenomegaly regression. In addition to reduction of spleen size, 16 (84.2%) of 19 patients had subjective improvement of splenomegaly-related symptoms. Figure 1b, c shows the computed tomography images of a patient with splenomegaly before and after radiotherapy with 4 Gy in four fractions, twice a week. Among 16 patients receiving splenic irradiation using a total dose with four fractions at twice a week, 2 patients showed significant improvement of splenomegaly or symptoms 1 week after starting treatment. However, three patients with symptomatic splenomegaly that were initially responsive to splenic irradiation were referred for re-irradiation for progressive disease with symptoms of splenomegaly after completion of the first course of splenic irradiation. The median interval between two treatment courses was 3 months. No patients underwent salvage surgical splenectomy for progressive splenomegaly.

Among 19 patients receiving splenic irradiation, 6 patients had a thrombocytopenia prior to radiotherapy. For these six patients, we observed a hematological response to splenic irradiation with improvement of thrombocytopenia in four patients. For these four responders, we found an average 41.7%

increase in platelet counts from baseline (mean \pm standard deviation of values before versus after radiotherapy, $3.6 \pm 1.9 \times 10^4$ versus $5.1 \pm 2.5 \times 10^4$; two-sided paired *t* test, *P* value = 0.025) (Table 1). The toxicity of splenic irradiation for these patients was limited to myelosuppression. Three patients developed grade 2 leukopenia 1 week after splenic irradiation. Prolonged life-threatening cytopenia was not recorded in these three patients (Supplementary Table 2). Of all 19 patients, 1 patient did not complete the full course of splenic irradiation because the patient experienced graft-versus-host disease-related diarrhea because of previous allograft transplantation for myelofibrosis. There were no other toxicities of grade 3 or above reported during or after splenic irradiation.

Considering that the extent of splenomegaly resulting from hematologic malignancies, most from myelofibrosis, caused constitutional symptoms, pain, cytopenia, and potential morbidity [9], splenic irradiation was previously used to treat patients with symptomatic splenomegaly. The effect of whole-spleen radiotherapy to relieve symptoms and improve the hemogram has been speculated to result from the deleterious effects of radiotherapy on neoplastic cells in the spleen [6] and

Table 1 Treatment response of splenic irradiation

Prior radiotherapy	Post radiotherapy	Response rate
Clinical features		
Splenomegaly (<i>n</i> = 19)	Spleen shrinkage (<i>n</i> = 18)	94.7%
Symptoms: pain (<i>n</i> = 19)	Pain relief (<i>n</i> = 16)	84.2%
Hematologic features		
Thrombocytopenia (<i>n</i> = 6)	Improvement of thrombocytopenia (<i>n</i> = 4)	66.7%
Platelet count/ μ L (average \pm SD; range)		<i>P</i> value
Total 6 patients		0.078*
$5.5 \pm 3.3 \times 10^4$; 2.1–9.6 $\times 10^4$	$6.5 \pm 2.4 \times 10^4$; 3.7–9.4 $\times 10^4$	
Responders (<i>n</i> = 4)		0.025*
$3.6 \pm 1.9 \times 10^4$; 2.1–6.3 $\times 10^4$	$5.1 \pm 2.5 \times 10^4$; 3.7–8.8 $\times 10^4$	

SD standard deviation, RT radiation therapy

*Two-tailed paired *t* test

Table 2 Published results of splenic irradiation for splenomegaly

Reference	Patient number	Dose (cGy)	Fraction size (cGy)	Response rate	Note
Wagner [15] (1986)	17	15–650	15–100	71% pain relief 65% spleen shrinkage	Majority of radiotherapy was delivered via telecobalt Co-60 or 6-MV photon
Elliott [6] (1999)	18	277.5	10–50	96% pain relief 94% spleen shrinkage	High morbidity rate: 26% life-threatening cytopenia
Kriz [9] (2011)	122	30–1600	10–200	75% pain relief 77% spleen shrinkage 74% hematological response	30% patients received telecobalt Co-60
Bruns [16] (2014)	5	300	50	80% pain relief 50% spleen shrinkage	Patients received splenic irradiation due to congestive splenomegaly
Ishibashi [8] (2015)	8	175–3000 (175–640 for MF, 50–3000 for NHL)	20–200 (20–100 for MF, 150–200 for NHL)	83% pain relief 83% spleen shrinkage	Poor response for NHL

MF myelofibrosis, NHL non-Hodgkin lymphoma

cytokine production and immune modulation [13, 14] from radiotherapy-induced changes of lymphocyte subsets.

Variations in radiation doses used in splenic irradiation, ranging from 15 to 3050 cGy, have been reported in previous series [6, 8, 9, 15, 16] (Table 2). Ishibashi et al. reviewed the response and toxicity of splenic irradiation in five patients with idiopathic myelofibrosis (radiotherapy dose ranged from 175 to 640 cGy), demonstrating relief of symptoms for myelofibrosis at the minimal dose of 175 cGy [8]. In analyses of a large series of 122 patients with chronic lymphoid and myeloid malignancies accompanied by splenomegaly, Kriz et al. [9] reported that splenic irradiation (a total of 246 courses) using a total dose per treatment course ranging from 30 to 1600 cGy (10–200 cGy per fraction) resulted in pain relief in 74.8% and 50% reduction of spleen size in 77% of radiotherapy courses.

Post-treatment complications of splenic irradiation are crucial issues in clinically caring for patients with underlying hematologic malignancies. Elliott et al. reviewed 23 patients with myelofibrosis with myeloid metaplasia who received splenic irradiation (50 courses, radiation dose ranged from 30 to 1365 cGy with a median of 277.5 cGy) for symptomatic splenomegaly and showed that the objective response rate of decreasing spleen size was 93.9% (46 courses), whereas the rate of significant cytopenia was up to 43.5% (occurring in 16 of the 50 courses) [6]. Notably, in their study, prolonged, life-threatening pancytopenia after a single course of splenic irradiation (doses ranged from 95 to 600 cGy) occurred in six patients (26%), and hemorrhage or sepsis occurred in three patients (13%) [6]. These nine patients subsequently underwent splenectomy; however, one-third of patients experienced postoperative morbidity of intra-abdominal hemorrhage [6]. In our series with low-dose splenic irradiation, three patients (16%) developed grade 2 leukopenia without prolonged life-threatening cytopenia after adequate monitoring and intensive care.

In summary, our results indicated that low-dose splenic irradiation with a median dose of 4 Gy, two fractions a week, using modern radiotherapy techniques resulted in a better response rate of thrombocytopenia and in symptom relief and a lower rate of adverse effects for patients with myelofibrosis. However, use of a sonography-assisted tool [17] for assessment of the spleen size will be the next step towards more objective evaluating of the response of splenomegaly reduction to splenic irradiation for patients with myelofibrosis.

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Compliance with ethical standards

The study protocol was approved by the Research Ethical Committee of National Taiwan University Hospital (NTUH: 201410063RINB). The patients' medical data were anonymized prior to access and analysis. The institutional review board has waived the need for written informed consent from study subjects because all potentially patient-identifying information was removed prior to data analysis.

Conflict of interest The authors declare that they have no conflict of interest.

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