

Revised Manuscript (Manuscript No. BJR-D-11-00114)

CT and MRI findings correlate with the time-course of unresectable cavernous hemangioma of the liver after fractionated radiotherapy

Short title: Hepatic hemangioma after fractionated RT

Abstract

We present the case of a 79-year-old woman with symptomatic cavernous hemangioma of the liver. She had experienced progressive right lateral abdominal pain for years despite increased painkiller use. As surgical resection or transarterial embolisation was not recommended because of her old age, cardiovascular comorbidities, and large tumour size, the patient was treated with 3-dimensional conformal radiotherapy (RT) with a total dose of 30 Gy in 15 fractions. Following RT, her painkillers were tapered from the third month, and complete symptomatic remission was achieved after the ninth month. The measured tumour volume from serial images pre-RT and 3, 9, and 15 months post-RT was 400, 372, 185, and 140 mL, respectively. The most dramatic volumetric reduction was found between 3 and 9 months post-RT, whereas the change before or after this period was minimal. The time-course of the radiological volumetric changes correlated with that of the clinical symptoms. In addition, the observed vascular changes on serial imaging studies were consistent with the assumed radiobiological effects after fractionated RT.

Introduction

Hepatic hemangiomas are the most common benign neoplasms of the liver, with an estimated prevalence of 0.4–20% [1–4]. Tumours larger than 5 cm are categorized as giant hemangiomas [5, 6] and may give rise to clinical symptoms. Patients with progressive abdominal discomfort or tumour enlargement should be considered for surgical resection, which is the treatment of choice in such patients [7, 8]. For patients with unresectable tumours or existing co-morbidities, radiotherapy (RT) may provide benefits in suspending tumour growth and relieving symptoms [9–12], even though the optimal RT dose scheme is not well defined and the comprehensive radiobiological effect is not clearly understood. However, RT is rarely recommended as a first-line therapy due to the concern of treatment-related liver toxicity and the long-term potential for secondary malignancies [9], and is generally reserved for treatment of massive hepatic hemangiomas associated with intractable congestive heart failure or hyperconsumptive coagulopathy in paediatric patients [9, 13, 14]. There is a lack of study regarding the time-course of hepatic hemangioma changes after irradiation; we here report the evolution of radiographic findings and clinical symptoms for a patient with hepatic hemangioma treated with fractionated RT.

Case history

In December 2004, a 76-year-old woman was transferred to Wang-Fang Hospital because she had experienced intermittent right lateral abdominal fullness for many years. She had a previous history of hypertension and coronary artery disease. Physical examination showed tenderness at the right upper quadrant of the abdomen. Ultrasound revealed an 8-cm mixed echoic mass at the right lobe of the liver. Magnetic resonance imaging (MRI) demonstrated a large lobulated mass in the right

lobe of the liver. The lesion had low signal intensity on T₁-weighted images and became hyperintense on T₂-weighted analogues. Furthermore, the tumour showed progressive gadolinium enhancement from peripheral to central areas. On the basis of the imaging study, the patient was diagnosed with giant cavernous hemangioma of the liver. As surgical resection or transarterial embolisation was not recommended because of her old age, cardiovascular co-morbidities, and large tumour size, it was suggested she undergo regular follow-up with pain control.

In October 2008, she was referred to radiation oncologists due to worsening of the right lateral abdominal pain despite opioid use. Using the visual analogue scale (VAS), the recorded pain score was 3 out of 10. The follow-up MRI showed substantial enlargement of the hemangioma (size: 13 x 11 x 5 cm). Liver function tests and tumour marker examination, including alpha-fetoprotein and carcinoembryonic antigen, showed values within the normal range. After multidisciplinary discussion, the hemangioma was treated with 3-dimensional conformal RT with a total dose of 30 Gy in 15 fractions prescribed to the 95% isodose curve. Tumour volume definition was based on contrast-enhanced computed tomography (CT). The visible tumour area on the image was delineated as the gross target volume (GTV), and a 5-mm margin was added to develop the clinical target volume (CTV). The planning target volume was defined as the CTV plus a 5–10-mm margin for tumour motion and setup uncertainties. The organs at risk, such as the normal liver, intestine, and spinal cord, were contoured. The measured pre-treatment GTV was 400 mL. The normal liver volume was 841 mL, and the mean normal liver dose was 15.8 Gy. The RT course was given over 21 days without interruption. Treatment-related acute and late toxicities were scored according to the Common Terminology Criteria for Adverse Events version 3.0 [15]. Except for grade 1 increases in aspartate aminotransferase

and alanine aminotransferase, detected in the third week of RT, the patient tolerated the treatment course well, without any complaint. She underwent imaging and liver function studies 3 months after RT and 6 months thereafter. No late complications such as radiation-induced liver disease were observed.

Her painkillers were tapered from the third month after treatment, and complete symptomatic remission (VAS: 0/10 without medication) was achieved after the ninth month following RT. The measured tumour volume at 3, 9, and 15 months after treatment was 372, 185, and 140 mL, respectively. The most dramatic volumetric change was found between 3 and 9 months post-RT. The time-course of the radiological volumetric changes correlated with that of the clinical symptoms. In addition, the observed vascular changes on serial imaging studies (Figure 1) were consistent with the assumed radiobiological effects after fractionated RT.

Discussion

A cavernous hemangioma is composed of cavernous vascular spaces of various sizes, lined by a single layer of endothelium. Although the biological mechanisms underlying the treatment efficacy of RT for hemangioma remain undetermined [16], damage to vascular endothelial cells and smooth muscle cells is generally assumed to play a key role in the radiation effects, leading to vascular thrombosis, necrosis, and fibrosis. These histological findings are regarded as late effects of RT based on the turnover time of the 2 cell types [17]. Nonetheless, it should be pointed out that radiation-induced vascular damage is not only dependent on the target cells, but also on the RT strategy used. The pathogenesis of late RT effects on vessels has been assessed in various experimental animal models, predominantly involving single dose or hypofractionated irradiation. Thus far, there is no clear conclusion regarding the

correlation between the vascular changes and the time-course of tumour shrinkage after fractionated RT [18]. According to the experience of radiosurgery in cerebral arteriovenous malformation (AVM), it is believed that the obliteration of the vasculature is a consequence of endothelial cell proliferation, progressive wall thickening, and eventual luminal closure [19]. Although it is generally accepted that RT-induced vascular occlusion occurs between 1 and 2 years following radiosurgery or hypofractionated RT [20, 21], the reported time-course of AVM shrinkage has been shown to vary considerably, and radiological findings have shown that vascular obliteration may occur as early as 4 months [22] or as late as 5 years after RT [23].

Compared with hypofractionated RT, no previous clinical study has described the correlation between volumetric tumour changes and clinical findings in conventional fractionated RT. This report is the first to show that the radiological changes induced in a hepatic hemangioma are associated with the time-course of clinical findings following fractionated RT. From a pathological point of view, a previous study suggested that the sequential histopathological changes in hepatic vessels after fractionated RT could be divided into 3 stages [24]. These stages are as follows: (1) acute stage: interstitial oedema of the vascular endothelium develops, leading to panlobular congestion within 6 months; (2) transient subacute stage: organising changes occur in the central vein, which may progress to partial obliteration; (3) chronic stage: sclerosis or thrombosis of hepatic arterioles and portal tissues takes place against the healing process, which occurs after 6 months. The radiological findings observed in this patient support the above histopathological processes. The 3-month post-RT CT study showed engorged vessels and peripheral oedema of the hepatic hemangioma, which correlates with the histopathological 'acute stage'. The 9- and 15-month post-RT images revealed increasing non-enhancing components within

the lesion, which was compatible with progressing thrombotic changes in the irradiated vessels. These findings may represent the late effects of RT. Subsequent images revealed that there was a dramatic reduction in tumour volume between 3 and 9 months post-RT, whereas the change before or after this period was minimal. In addition, the volumetric changes observed matched the time-course of clinical symptoms after fractionated RT.

It is generally believed that arterial damage occurs at a cumulative RT dose of 50–70 Gy delivered in conventional fractionation patterns, whereas capillaries are vulnerable to irradiation damage when the dose is above 40 Gy [17]. In contrast, previous studies have shown satisfactory results in terms of tumour volume reduction or symptom relief when a total dose of 20–30 Gy was prescribed for hepatic hemangiomas by conventional RT [9, 10]. In this patient, a good response was also achieved with a similar RT dose. These findings imply that the vasculature of hepatic hemangiomas is more susceptible to radiation damage than normal vessels [17]. Perhaps, the vasculature of hepatic hemangiomas is not as well structured as normal vessels.

As liver toxicity is the major concern associated with RT for hepatic hemangioma, the prescribed dose was administered with certain constraint. In the future, high-precision RT techniques with altered fractionated studies should be performed to determine the optimal RT strategy. Although various imaging methods including Doppler ultrasound, CT, and MRI have been reported feasible to study vascular physiology [25], more comprehensive and consistent radiological studies using dynamic imaging assessments should be encouraged to further clarify the time-course of the biological effects in irradiated hepatic hemangioma.

Conclusion

Fractionated RT can provide an alternative treatment for unresectable cavernous hemangiomas. Based on previous studies and our report, local control is satisfactory following a total dose of 30 Gy. This report is the first to show that the radiological changes induced in a hepatic hemangioma are associated with the time-course of clinical findings following fractionated RT. In particular, the observed vascular changes were correlated with the assumed radiobiological effects. Thus, CT or MRI can be utilised to monitor the subsequent radiobiological effects on hepatic vessels after fractionated RT.

References

1. Karhunen PJ. Benign hepatic tumours and tumour like conditions in men. *J Clin Pathol.* 1986 Feb;39(2):183-8.
2. Gandolfi L, Leo P, Solmi L, Vitelli E, Verros G, Colecchia A. Natural history of hepatic haemangiomas: clinical and ultrasound study. *Gut.* 1991 Jun;32(6):677-80.
3. Ishak KG, Rabin L. Benign tumors of the liver. *Med Clin North Am.* 1975 Jul;59(4):995-1013.
4. Gilon D, Slater PE, Benbassat J. Can decision analysis help in the management of giant hemangioma of the liver? *J Clin Gastroenterol.* 1991 Jun;13(3):255-8.
5. Adam YG, Huvos AG, Fortner JG. Giant hemangiomas of the liver. *Ann Surg.* 1970 Aug;172(2):239-45.
6. Grieco MB, Miscall BG. Giant hemangiomas of the liver. *Surg Gynecol Obstet.* 1978 Nov;147(5):783-7.
7. Yoon SS, Charny CK, Fong Y, Jarnagin WR, Schwartz LH, Blumgart LH, et al. Diagnosis, management, and outcomes of 115 patients with hepatic hemangioma. *J Am Coll Surg.* 2003 Sep;197(3):392-402.
8. Erdogan D, Busch OR, van Delden OM, Bennink RJ, ten Kate FJ, Gouma DJ, et al. Management of liver hemangiomas according to size and symptoms. *J Gastroenterol Hepatol.* 2007 Nov;22(11):1953-8.
9. Gaspar L, Mascarenhas F, da Costa MS, Dias JS, Afonso JG, Silvestre ME. Radiation therapy in the unresectable cavernous hemangioma of the liver. *Radiother Oncol.* 1993 Oct;29(1):45-50.
10. Biswal BM, Sandhu M, Lal P, Bal CS. Role of radiotherapy in cavernous hemangioma liver. *Indian J Gastroenterol.* 1995 Jul;14(3):95-8.
11. McKay MJ, Carr PJ, Langlands AO. Treatment of hepatic cavernous

- haemangioma with radiation therapy: case report and literature review. *Aust N Z J Surg.* 1989 Dec;59(12):965-8.
12. Mascarenhas F, Gaspar L, Da Costa MS, Afonso JG, Silvestre ME. [Effectiveness of radiotherapy in non-resectable cavernous hemangioma of the liver]. *Acta Med Port.* 1989 May-Jun;2(3):147-53.
 13. Cohen RC, Myers NA. Diagnosis and management of massive hepatic hemangiomas in childhood. *J Pediatr Surg.* 1986 Jan;21(1):6-9.
 14. Iyer CP, Stanley P, Mahour GH. Hepatic hemangiomas in infants and children: a review of 30 cases. *Am Surg.* 1996 May;62(5):356-60.
 15. Kjellberg RN, Hanamura T, Davis KR, Lyons SL, Adams RD. Bragg-peak proton-beam therapy for arteriovenous malformations of the brain. *N Engl J Med.* 1983 Aug 4;309(5):269-74.
 16. Brady LW. Radiotherapy for non-malignant disorders. Contemporary concepts and clinical results. Berlin, Germany: Springer, 2008.
 17. Hall, EJ. Radiobiology for the Radiologist, 5th edition. Philadelphia, USA: Lippincott Williams & Wilkins, 2006.
 18. Joiner M, Basic clinical radiobiology. 4th edition., London, UK: Hodder Arnold, 2009.
 19. Steiner L, Lindquist C. Radiosurgery in cerebral arteriovenous malformation. In: Tasker RR, editor. *Neurosurgery: State of Art Reviews, Stereotactic Surgery.* Philadelphia, USA: Hanley and Belfus, Inc, 1987; vol 2, 329–336.
 20. Leksell DG. Special stereotactic techniques: stereotactic radiosurgery. In: Heilbrun MP, editor. *Concepts in Neurosurgery: Stereotactic Neurosurgery (vol 2).* Baltimore, USA: Lippincott Williams & Wilkins, 1988:195–209.
 21. Kjellberg RN, Hanamura T, Davis KR, Lyons SL, Adams RD. Bragg-peak

proton-beam therapy for arteriovenous malformations of the brain. *N Engl J Med.* 1983 Aug 4;309(5):269-74.

22. Lunsford LD, Kondziolka D, Flickinger JC, Bissonette DJ, Jungreis CA, Maitz AH, et al. Stereotactic radiosurgery for arteriovenous malformations of the brain. *J Neurosurg.* 1991 Oct;75(4):512-24.
23. Yamamoto M, Jimbo M, Kobayashi M, Toyoda C, Ide M, Tanaka N, et al. Long-term results of radiosurgery for arteriovenous malformation: neurodiagnostic imaging and histological studies of angiographically confirmed nidus obliteration. *Surg Neurol.* 1992 Mar;37(3):219-30.
24. Tefft M, Mitus A, Das L, Vawter GF, Filler RM. Irradiation of the liver in children: review of experience in the acute and chronic phases, and in the intact normal and partially resected. *Am J Roentgenol Radium Ther Nucl Med.* 1970 Feb;108(2):365-85.
25. Laking GR, West C, Buckley DL, Matthews J, Price PM. Imaging vascular physiology to monitor cancer treatment. *Crit Rev Oncol Hematol.* 2006 May;58(2):95-113.

Figure 1. A 70-year-old woman was diagnosed with cavernous hemangioma of the liver and received fractionated radiotherapy (RT). (A) Contrast-enhanced coronal and (B) axial T₁-weighted magnetic resonance imaging (MRI) scans before RT show a lobulated tumour mass (arrow), with persistent enhancement in the delayed phase, in the right lobe of the liver. (C, D) Follow-up contrast-enhanced computed tomography (CT) images 3 months after RT show engorged vessels (thick arrow) and peripheral oedema (thin arrow) of the tumour. (E, F) Follow-up contrast-enhanced CT images 9 months after RT show a gradual increase in non-enhancing components (arrow) within the tumour, compatible with thrombosed vessels. (G, H) Follow-up contrast-enhanced T₁-weighted MRI images (delayed phase) 15 months after RT show a remarkable increase in non-enhancing components (arrow) within the tumour, compatible with interval progression of thrombosed vessels.