CASE REPORT

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

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ABSTRACT. We present the case of a 79-year-old female with symptomatic cavernous haemangioma of the liver. The patient had experienced progressive right lateral abdominal pain for years despite increased painkiller use. Surgical resection or transarterial embolisation was not recommended because of the patient's age, cardiovascular comorbidities and large tumour size. Therefore, the patient was treated with 3-dimensional conformal radiotherapy (RT) with a total dose of 30 Gy in 15 fractions. Following RT, the 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 ml, 372 ml, 185 ml 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.

Received 27 January 2011
Revised 13 May 2011
Accepted 13 June 2011

DOI: 10.1259/bjr/74795623

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Radiology

Hepatic haemangiomas 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 categorised as giant haemangiomas [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 comorbidities, radiotherapy (RT) may provide benefits in suspending tumour growth and relieving symptoms [9–12], although 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 owing to the concern of treatment-related liver toxicity and the long-term potential for secondary malignancies [9]. It is generally reserved for treatment of massive hepatic haemangiomas associated with intractable congestive heart failure or hyperconsumptive coagulopathy in paediatric patients [9, 13, 14]. There is a lack of studies regarding the time-course of hepatic haemangioma changes after irradiation; we report the evolution of radiographic findings and clinical symptoms for a

patient with hepatic haemangioma treated with fractionated RT.

Case history

In December 2004, a 76-year-old female was transferred to Wang-Fang Hospital because she had experienced intermittent right lateral abdominal fullness for many years. The patient had a history of hypertension and coronary artery disease. A physical examination showed tenderness at the right upper quadrant of the abdomen. An ultrasound revealed an 8 cm mixed echoic mass at the right lobe of the liver. MRI demonstrated a large lobulated mass in the right lobe of the liver. The lesion had low signal intensity on T_1 weighted images and became hyperintense on T_2 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 haemangioma of the liver. Surgical resection or transarterial embolisation was not recommended because of the patient's age, cardiovascular comorbidities and large tumour size. It was suggested the patient undergo regular follow-up with pain control.

In October 2008, the patient was referred to radiation oncologists due to worsening of the right lateral abdominal pain despite opioid use. Using the visual analogue

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scale (VAS), the recorded pain score was 3 out of 10. The follow-up MRI showed substantial enlargement of the haemangioma (size: $13 \times 11 \times 5$ cm). Liver function tests and tumour marker examination, including alpha-fetoprotein and carcinoembryonic antigen, showed values within the normal range. Following a multidisciplinary discussion, the haemangioma 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 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 set-up 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 at 6 month intervals thereafter. No late complications such as radiation-induced liver disease were observed.

The patient's 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 following treatment was 372 ml, 185 ml 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 following fractionated RT.

Discussion

A cavernous haemangioma 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 haemangioma 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 two cell types [17]. However, 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]. From previous radiosurgeries with 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. 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 haemangioma are associated with the time-course of clinical findings following fractionated RT. From a pathological point of view, a previous study suggested the sequential histopathological changes in hepatic vessels after fractionated RT could be divided into three 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 haemangioma, 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 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 haemangiomas 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 haemangiomas is more susceptible to radiation damage than normal vessels [17]. Perhaps, the vasculature of hepatic haemangiomas is not as well structured as normal vessels.

Liver toxicity is the major concern associated with RT for hepatic haemangioma, so 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

Figure 1. A 70-year-old female was diagnosed with cavernous haemangioma of the liver and received fractionated radiotherapy (RT). (a) Contrast-enhanced coronal and (b) axial T_1 weighted 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 CT images 3 months following RT show engorged vessels (thick arrow) and peripheral oedema (thin arrow) of the tumour. (e, f) Follow-up contrast-enhanced CT images 9 months following RT show a gradual increase in non-enhancing components (arrow) within the tumour, compatible with thrombosed vessels. (g, h) Follow-up contrast-enhanced T_1 weighted MRI images (delayed phase) 15 months following RT show a remarkable increase in non-enhancing components (arrow) within the tumour, compatible with interval progression of thrombosed vessels.

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 haemangioma.

Conclusion

Fractionated RT can provide an alternative treatment for unresectable cavernous haemangiomas. 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 the radiological changes induced in a hepatic haemangioma 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. Therefore, CT or MRI can be used to monitor the subsequent radiobiological effects on hepatic vessels after fractionated RT.

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