Characteristic Uptake Pattern of Bone Scintigraphy in Patients with Hepatocellular Carcinoma Following Treatment with High-Intensity Focused Ultrasound

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Abstract

Purpose This study retrospectively reviews the characteristic bone scintigraphic findings in 18 patients with hepatocellular carcinoma (HCC) following treatment with high-intensity focused ultrasound (HIFU). A potential complication of HIFU is damage to the tissues along the path of the ultrasound beam and structures superficial to the lesion of interest.

Methods Patients with hepatocellular carcinoma who underwent a bone scan between 1st December 2005 and 31st December 2011 were considered for this study. Among these patients, only those who had bone scans after the HIFU treatment were included. The time between HIFU treatment and bone scans, HIFU energy, HCC sites, tumour sizes and related radiological findings were evaluated.

Results In total, 20 bone scans of 18 patients were reviewed. Of these scans, two patients were normal; three patients showed decreased uptake, four patients showed increased uptake and nine patients showed mixed uptakes of the bony

tracer in their rib cages. The defects were located in the anterior, lateral, anterolateral or posterolateral aspects of the rib cage. The majority of those cold defects were in the right anterior rib cages. SPECT/CT was used to localise the decreased uptake in ribs. The magnetic resonance imaging in individual patients invariably showed ill-defined rim enhancement along the right chest wall, signifying chest wall injury.

Conclusions The results showed that tissue ablation using HIFU caused tissue injury along the pathway of high-intensity ultrasound beams. The harm to tissues is presented as photopenic area on the rib cages due to necrosis or hot spots due to rib fractures in the bone scan. Since these cold defects are subtle, they are easily overlooked or mistaken as aggressive bony metastasis.

Keywords Hepatocellular carcinoma · Bone scan · High-intensity focused ultrasound

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Introduction

High-intensity focused ultrasound (HIFU) was first introduced in the early 1940s by Lynn et al. [1] for the propulsion of oil and melting of paraffin. Nowadays, HIFU has been successfully applied in the treatment of solid tumours of the bone, brain, breast, liver, pancreas, rectum, kidneys, testes, prostate and uterus [2]. HIFU uses high-amplitude focused acoustic waves to heat and ablate selected tissue at a selected depth within the body. HIFU produces focused ultrasound waves by using a transducer. The ultrasound energy is attenuated during its passage through tissue paths; some are absorbed and some are scattered as heat. A rapid temperature increase ($>56^{\circ}\text{C}$) induces coagulation necrosis. At the same time, particle vibration caused by the high intensity ultrasound beam produced mechanical disruption of intracellular membranes [3]. Intracellular water vaporises to form microbubbles, producing shock waves that can mechanically lead to the

breakdown of tumour cells. In theory, the ablation beams target a specific region without damaging nearby structures. However, as reported in previous studies, HIFU induced skin burns and pain in the treatment region, neurapraxia of stomach and intestines, rarely developed superior mesenteric infarction and perforation in terminal ileum [4]. Jung et al. [5] showed that the ultrasound heat could cause third-degree burn, necrosis of the ribs along the main ultrasound beam path, rib fractures and other complications such as biliary obstruction, pneumothorax and fistula formation.

In this study, we highlight the observations regarding the distinctive scintigraphic patterns in patients with hepatocellular carcinoma treated with HIFU and associate the clinical significance of abnormal uptake in the rib cage in this specific group of patients.

Materials and Methods

A retrospective study of patients with bone scintigraphy and previous history of HIFU treatment for hepatocellular carcinoma was conducted between 1st December 2005 and 31st December 2011 at our institute. Bone scans performed after the HIFU for the evaluation of bony metastases were included. The patient population consisted of 18 patients (3 women, 15 men; age range 48–81 years). None of our patients previously had rib resections or documented prior trauma to the chest wall according to their case notes.

Bone scintigraphy was performed 3–4 h after the administration of Tc-99m methylene diphosphonate (20–25 mCi) using a gamma camera (Hawkeye 4; GE Medical, Waukesha, WI, USA) equipped with a low-energy high-resolution collimator.

Table 1 Characterisation of the lesions in the rib cage in 18 patients

Patient	Sex	Age	Lesion sites (R)	Bone scan grading	Date from HIFU treatment
1	M	80	R lat 7th–9th ribs	2	24 months
2	M	71	R lat 7th–10th ribs	0	25 months
3	F	65	R lat 7th rib	2	23 months
4	F	71	R ant 7th–8th ribs	0	2 months
			R lat 9th–10th, R post 12th ribs	2	2 months
5	M	69	R ant and anterolateral 7th–10th ribs	0	4 months
			R lat 4th, anterior end of R 5th–6th ribs	2	4 months
6	M	54	R lat 8th ribs	0	3 months
			R lat 8th–9th ribs	2	3 months
7	M	56	R posterolateral 9th–10th ribs	0	2 months
			R post 9th–10th ribs	2	2 months
8	M	55	R lat 6th–8th ribs	0	2 months
					10 months
			R ant and lat 5th–9th ribs	2	2 months
					10 months
9	M	69	R lat 6th–8th ribs	2	9 months
10	M	66	Normal	1	18 months
11	M	69	R ant 8th–10th ribs	0	16 months
			R lat 7th and 9th ribs	2	16 months
			R ant 8th–10th ribs	0	21 months
			R lateral 7th ribs	2	21 months
12	M	81	R anterolat 8th–9th ribs	0	8 months
			R lat 9th rib	2	8 months
13	M	69	R lat 9th & R posterolateral 10th ribs	0	1 month
			Ant end of R 7th–8th ribs	2	1 month
14	M	63	R ant & lat 7th–8th ribs	0	6 days
			R lat 9th–10th ribs	2	6 days
15	F	65	R ant 2nd, 4th, 5th, 8th, & 9th ribs	2	9 months
16	M	48	R posterolateral 9th–10th ribs	0	2 months
17	M	65	Normal	1	2 months
18	M	55	R ant 5th–6th ribs	0	15 days
					5 months

The scan included both anterior and posterior whole-body imaging (scan speed 10 cm/min; matrix $256 \times 1,024$). Spot views were used in selected cases (matrix 256×256). For each static view, 600 kcounts were collected. Additional SPECT (single photon emission computed tomography) or SPECT/CT scans were obtained at the discretion of the attending nuclear medicine physicians. Bone scans were interpreted retrospectively by a nuclear medicine physician, who assigned a three-point scintigraphic score based on the uptake by the rib cage compared with that of the sternum:

- 0: decreased
- 1: normal
- 2: increased

HIFU Treatment

The treatment was performed using a high-intensity focused ultrasound system (Chongqing, Haifu, China). The sites of hepatocellular carcinoma, tumour sizes, date of HIFU prior to bone scan, energy and duration were documented.

Other Imaging Findings

The radiographs, CT or MRI after the HIFU treatment were obtained in all patients. We evaluated and correlated the image findings with the bone scan results.

Results

Table 1 summarises the demographic and scintigraphic data. The time interval between the HIFU treatment and bone scintigraphy ranged from 6 days to 25 months. There were 18 patients with 20 bone scans performed. Except for two patients with normal scan findings, the rest of the patients showed abnormal uptake in their bone scans. Three patients showed a purely decreased uptake of bony tracer in the right rib cage (Fig. 1). The cold defects were located in anterior, lateral, anterolateral or posterolateral aspects. The majority of the photopenic defects were in the right anterior rib cage, along the right 5th–11th ribs, signifying the different routes of HIFU therapy. The intensity of the lesions varied from absent uptake to only minimally visible. The cold defects were usually segmental and involved consecutive ribs. Two patients underwent a thorax or abdomen SPECT/CT (Fig. 2). The results clearly localised the decrease uptake in the corresponding ribs, similar to those of planar bone scans. The decrease in intensity began as early as 6 days after the HIFU treatment, as seen in patient number 14, and the effect may last as long as 25 month, as witnessed in patient number 2.

Fig. 1 **a** WBS images. **b** Decreased uptake in right anterior 5th–6th ribs as indicated by arrows

Four patients showed focal increased tracer uptake in rib cages and nine patients showed mixed focal activity. Among these 13 patients, one was consistent with bone metastasis, nine were consistent with trauma/rib fractures and there were three patients with bone scan findings that could not differentiate rib fractures from metastasis. A follow-up bone scintigraphy after 5 months was conducted in one patient with equivocal findings. The scintigraphy showed partial resolution of the hot spots in favour of fractures/trauma. Two patients with no abnormal uptake on the rib cage only had whole-body (AP) images performed.

Fig 2 **a** Planar whole-body Tc-99m MDP imaging in oblique view shows decreased uptake in the right lateral 10th rib (*arrowhead*) and increased linear activity in bilateral rib cage. The latter was interpreted as equivocal for either rib trauma/fracture or bone metastasis. Note the patchy increased uptake in right humerus is consistent with site of pathological fracture. **b** SPECT/CT demonstrates physiological bony tracer uptake in the spine, ribs and clearly localised the decreased uptake in the right lateral 10th rib (*arrowhead*). Increased uptake in the anterior ends of right 7th–8th ribs are likely trauma related

Although few cases were examined, 67 % of the cases (12/18) showed decreased bony tracer accumulation from a few days up to 25 months post HIFU treatment. Figure 3 shows the transaxial T1-weighted and gadolinium-enhanced MR images obtained in patient 11, who had undergone HIFU ablation for hepatocellular carcinoma. Images obtained a month after HIFU showed a hyperintense rim and hypointense centre of segment VII/VIII of the liver. Poor margined rim enhancement along the right chest wall signified chest wall injury. It was noted that the ribs were located along the different ultrasound routes.

Fig 3 Images after HIFU: MRI shows hyperintense rim and hypointense centre of the right hepatic lobe and right chest wall oedema (*arrowhead*)

Discussion

High-intensity focused ultrasound (HIFU) produces focused acoustic energy of ultrasound beams that induced tissue destruction by coagulation necrosis [6]. Currently, HIFU is a treatment of choice for a variety of cancers, uterine fibroids and for treating heart arrhythmias. HIFU therapy ideally focused at a target tissue without interference to the shallower, non-targeted tissues. However, when the power of ultrasound was high, reflected ultrasound from ribs and bowel gas could produce thermal injury to the skin, subcutaneous tissues and muscles. As reported by Dubinsky et al. [7], the reflected waves in the bowel gas could produce burning of the abdominal wall and even bowel wall. It was once thought that ultrasound energy could not penetrate through the bones. Nevertheless, high-energy absorption at the interface of bone surface and incident beam could cause a significant temperature rise and induce bone necrosis as well as injury to adjacent tissues. Besides, the heat diffusion from the target site, inhomogeneities in the tissue path and patient movement during treatment all contributed to the possibility of unwanted tissue

damage. Our study showed that bone scan evidence of coagulative necrosis (present as cold defects) in the ultrasonic pathway as early as a few days after HIFU and up to 25 months after the treatment. An accurate diagnosis of bony necrosis could be made when focally decreased uptake is detected on oblique chest view. Planar scintigraphy was sufficient to detect any change in bone tracer uptake in the rib cages. However, the characteristic decreased uptake may be subtle and easily overlooked. Misinterpretation of the findings of decreased uptake as aggressive osseous metastasis could be minimised by SPECT fused with CT images.

We found that the uptake in the affected ribs had not returned to normal even after 25 months post HIFU treatment, indicating that the bone remodelling was substantially slow. The possible cause was due to decreased blood supply secondary to vessel injury. It also showed that bone scan can detect increased MDP activity in the ribs probably due to trauma caused by intervention or rib fractures that is a consequences of thermal injury. Evaluation of the SPECT/CT images in the bone windows for anatomical information, specifically to look for cortical break or callus formation that corresponded to the increased uptake caused by rib fractures, could significantly increase certainty in diagnosis. There also seems to be no direct relationship between the timing of the HIFU treatment and change in MDP uptake. The appearance of cold defects in rib cages occurred as early as 6 days and up to 25 months after HIFU.

Seo et al. [8] published a retrospective study on bone scan findings after HIFU treatment. According to that study, there was a 71.2 % diffusely decreased uptake of bone within the path of HIFU, with CA breast along the 2nd–5th ribs, hepatic tumour along 5th–11th ribs and 9th–10th ribs in pancreatic tumour. The distribution pattern of hepatic tumour group was similar to our study. However, Seo et al. included patients with various tumour types. Apart from the location, the lesions were usually segmental, with intensity varied from absent to low-grade uptake and typically involving consecutive ribs. Identification of this specific pattern may improve accuracy and avoid misinterpretation as aggressive bony metastasis. Furthermore, there were two patients who showed physiological distribution of tracer in the whole-body imaging. These two patients had not taken spot views on the right anterior oblique chest or left posterior oblique chest. The actual percentage of patients with decreased bony uptake might be underestimated.

Our study had limitations. Owing to the retrospective nature of the study, HIFU treatment field was not available for all patients. Besides, the effect of the wide time interval between

bone scan and HIFU should be considered (ranged from 6 days to 25 months). Nevertheless, 67 % of our patients had clear cold defects on the right rib cage as shown on bone scans. We also did our best to follow-up our patients by using MRI and bone scan whenever possible. As such, the nature of the rib lesions had been clarified sufficiently.

Conclusions

HIFU was a rapid, precise and non-invasive treatment modality for solid tumours, including hepatocellular carcinoma. There have been several studies addressing the use of HIFU for tumours with complications of burns, necrosis of the ribs along the main ultrasound beam paths and rib fractures. Our study result was in line with these studies. Recognition of a specific scintigraphic pattern for patients with previous HIFU treatment could improve the specificity of bone scan, without the need for further additional SPECT/CT or MRI studies for correlation.

Conflicts of Interest None.

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