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Originals

Splenomegaly and Tumor Marker Response Following Selective Internal Radiation Therapy for Non-Resectable Liver Metastases from Neuroendocrine Tumor

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SUMMARY

PURPOSE : The aim of this study was to investigate changes in spleen size, the level of chromogranin A as a tumor marker, and the relationship between these two parameters before and 3 months after selective internal radiation therapy (SIRT) for non-resectable liver metastases from neuroendocrine tumor (NET). Our first serious adverse event with this relatively new treatment is also discussed.

METHODS : A retrospective review of a prospective database identified patients with non-resectable liver metastases from NET who underwent SIRT between 2003 and 2007. Patients who underwent CT scans before and 3 months after treatment were included. The patients were divided into two groups : those with and without a 20 % or more increase in splenic volume on the CT scans. The percentages of patients showing a tumor marker response in the two groups were then compared

RESULTS : Fourteen patients were included in the present analysis. A tumor marker response was seen in 6 of 7 patients (85.7 %) who showed an increase in splenic volume of ＞20 %, and in 3 of 7 patients (42.9 %) without an increase in splenic volume ($p = 0.266$). There was one death as a result of oesophageal variceal bleeding due to portal hypertension at 9 months after treatment.

CONCLUSION : Splenic enlargement after SIRT may be associated with tumor marker response, although this could not be confirmed statistically in this study due to the small number of patients. Long-term splenomegaly and portal hypertension may be important complications of SIRT. This issue needs to be investigated further using a larger number of patients and longer follow-up.

Key Words : internal radiation therapy, SIRT, neuroendocrine tumor, liver metastasis, splenomegaly

INTRODUCTION

Liver metastases from neuroendocrine tumor (NET) represent a management dilemma, as many treatment options are available, including aggressive liver resection, transplantation, chemoembolisation, chemotherapy and hormonal therapy[1,2]. The decision as to which treatment will benefit each individual patient is far from simple, and requires a multidisciplinary approach[3]. Selective internal radiation therapy (SIRT) is currently being used to target non-resectable hepatic metastases with the aim of improving symptoms and prolonging survival[4]. We report our early results with SIRT for non-resectable liver metastases from

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Table 1 Splenic volume before and 3 months after SIRT in patients with neuroendocrine hepatic metastases, categorised into splenic volume increase of more than or less than 20 %

Group	Number of patients	Mean splenic volume (mL) before SIRT (range)	Mean splenic volume (mL) 3 months after SIRT (range)	Difference (mL) (95 % confidence interval)
＞20 % splenic volume increase	8	226 (92-485)	299 (111-599)	75 (27-118)
＜20 % splenic volume increase	8	289 (112-620)	259 (110-393)	30 (－40-100)

NET focusing particularly on changes in splenic volume and tumor marker response.

METHODS

We reviewed the records of all patients who had undergone SIRT for unresectable liver metastases from NET in a pilot study. All patients who had undergone CT scans at the baseline prior to, and 3 months after, SIRT were included in the present analysis. Splenic volume was calculated using a digitizer Tablet (Kurta 1s/one, Kurta Corporation, Phoenix, AZ). By using the known scale on the CT images, the specific area of the spleen was calculated on each slice, and all the slices were summed to estimate the volume of the spleen. Serum tumor marker levels at the baseline and at 3 months were also recorded. Chromogranin A (CgA) was used as the tumor marker, as this has been shown to be reliable for monitoring therapeutic outcome in patients with neuroendocrine tumors[5].

Patients were divided into two groups : those in whom splenic volume increased ≧ 20 %, and those in whom it increased ＜ 20 %. Statistical analysis was performed to assess any association between the change in splenic volume and a tumor marker response.

Statistical analyses were performed using SPSS v. 12.0 for Windows (SPSS). The paired sample t-test was used for comparison of continuous variables, and chi-squared test with Yates's correction and Fisher's exact test were used for categorical variables. Statistical significance was defined as $p < 0.05$.

RESULTS

A total of 29 patients with non-resectable liver metastases from NET were identified. Sixteen patients were included in the present analysis. Four patients were excluded because they had previously undergone splenectomy, and 9 patients did not undergo a CT scan at 3 months after SIRT.

Eight patients had an increase in splenic volume of ＞20 %, while the other 8 did not. In the patients with an increase in splenic volume of ＞20 %, the mean splenic volume at the baseline was 226 mL (range 92 mL－485 mL). At 3 months after SIRT the mean splenic volume was 299 mL (range 111 mL－599 mL ; mean difference 75 mL, 95 % CI, 27 mL－118 mL, $p = 0.007$). For the other 8 patients, the mean splenic volume at the baseline was 289 mL (range 112 mL－620 mL), and at 3 months after SIRT it was 259 mL (range 110 mL－393 mL ; mean difference 30 mL, 95 % CI, －40 mL－100 mL, $p = 0.348$) (Table 1). Unfortunately, 2 patients, one in each group, did not undergo repeat determination of the CgA level at 3 months after SIRT. Among the 7 patients with a splenic volume increase of ＞20 %, 6 (85.7 %) showed a tumor marker response. Three (42.9 %) of the 7 patients in the other group had a tumor marker response ($p = 0.266$) (Table 2).

One patient who died at 10 months after SIRT had a splenic size of 485 mL prior to treatment, and at 3 months after treatment the splenic size was 599 mL (the largest size in the study group). He remained well for 8 months, although multiple bone metastases were revealed by a pre-SIRT bone scan. He became jaundiced and his condition deteriorated with peripheral oedema, progressive ascites and weight loss. He was admitted to hospital at 9 months after SIRT with upper gastrointestinal bleeding and a duodenal ulcer, and oesophageal varices were noted at gastroscopy. He suffered further gastrointestinal bleeding, and repeat

Table 2 Number of patients with tumor marker response, categorised into those more than or less than 20 % increase in splenic volume

	Tumor marker response	No tumor marker response	Total patienfs
＞20 % splenic volume increase	6 (85.7 %)	1 (14.3 %)	7 (100 %)
＜20 % splenic volume increase	3 (42.9 %)	4 (57.1 %)	7 (100 %)

* p-value = 0.266

endoscopic evaluation revealed bleeding from grade 2 oesophageal varices. This bleeding was persistent despite sclerotherapy and Minnesota tube insertion, and the patient's condition continued to deteriorate with progression to multi-organ failure.

DISCUSSION

Patients with hepatic metastases from neuroendocrine tumor can show a variable clinical course. Some patients are particularly troubled by pain and endocrinopathy, while others are asymptomatic[3]. Liver resection is a potential treatment for these patients, both to extend life and palliate the symptoms, and the 5-year survival after liver resection has been reported to be around 60-80 %[6~9]. However, patients with ＞50 % liver involvement have a poor outcome despite these aggressive treatments. SIRT is currently under clinical trial at our institution for treatment of these patients. Previous reports have indicated that SIRT can cause hepatotoxicity and portal complications. One study, which reviewed SIRT with respect to hepatic toxicity in patients with diffuse somatostatin receptor-positive liver metastases, found that there was only a small chance of developing mild acute or subacute hepatic radiation injury[10]. There are very few published data on the effect of SIRT on the liver parenchyma and portal hemodynamics. One letter to the *Journal of Clinical Oncology* described one patient who had significant portal hypertension with a large number of collateral bleeding vessels, which necessitated abandoning liver resection following SIRT. It is interesting that in this case SIRT achieved down-staging of the liver metastases, but also resulted in extensive fibrosis of the liver parenchyma and resulting portal hypertension[11~13]. Portal hypertension was not present at the time of resection of the primary tumor.

We reviewed the change in the size of the spleen to gauge any effects of SIRT on portal hypertension. Moroz et al. also reported similar findings of splenic enlargement after SIRT, and postulated that splenic enlargement following SIRT and hepatic arterial infusion chemotherapy are due to portal hypertension caused by scarring within the liver as a consequence of radiation and chemical hepatitis, respectively[14].

In our small series, there was one serious adverse event that may have been related to SIRT. Although our results have insufficient statistical validity, they suggest that in patients who respond to treatment, SIRT does lead to an increase in splenic volume, indicative of underlying portal hypertension, and its associated complications. A further study with a larger number of patients and a longer follow-up will be needed.

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