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Determination of tumour vascularity using selective hepatic angiography as compared with intrahepatic-arterial technetium-99m macroaggregated albumin scan in hepatocellular carcinoma

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Abstract. A total of 51 patients with hepatocellular carcinoma (HCC) were studied to determine the tumour vascularity as determined by selective hepatic angiography (HAG) and by intrahepatic-arterial technetium-99m-labeled macroaggregated albumin (Tc^{99m}-MAA) scan. The tumour vascularity was graded on the HAG films by an interventional radiologist using a scale ranging from 1 (hypovascular) to 4 (extremely hypervascular). The grades of vascularity on HAG were grade 1 in 5 patients, grade 2 in 13 patients, grade 3 in 24 patients and grade 4 in 9 patients. The tumour vascularity on scintigraphy was determined by quantifying the count rates over the tumour and normal liver areas by an analog/digital gamma-camera, and the resultant tumour-to-normal ratio (T/N ratio) gave a quantitative measure of the vascularity. The range of the T/N ratio was 0.9 to 11.1, with a median of 3.7. There was no correlation between the tumour vascularity grading on HAG and the T/N ratio on the Tc^{99m}-MAA scan (Wilcoxon rank test, $P = 0.83$). Thus, we conclude that HAG cannot reveal the true vascularity nor reflect the T/N ratio in HCC.

Introduction

Hepatocellular carcinoma (HCC) is an aggressive and vascular tumour. Locoregional treatment using intrahepatic-arterial chemotherapy, chemoembolisation and selective internal radiation (SIR) with Lipiodol-I^{131} or Y^{90} microspheres is currently employed for the treatment of inoperable cases. The success of such treatments depends on the relative uptake and retention of the drugs or radioisotopes by the tumour relative to the normal liver (tumour-to-normal ratio or T/N ratio). The higher the T/N ratio, the better. The T/N ratio depends on the blood flow and vascularity of the tumour. This is especially important in internal radiation treatment because a poor T/N ratio may result in a sub-optimal dose to the tumour if too small a radioactive dose is given and, conversely, in radiation hepatitis if too large a dose is given [2].

The tumour vascularity also indirectly reflects the volume of the vascular space within the tumour into which the radioactive isotopes or chemoembolisation substances can enter. A hypovascular tumour may not have enough vascular space to contain the full amount of a therapeutic substance introduced into the hepatic artery, and the excess tends to leak into the normal parts of the liver or overflow into the extrahepatic circulation and the transported to other organs.

Tumour vascularity is usually assessed by HAG, which gives only a subjective and qualitative estimation. Massive and solitary HCC commonly has a thin hypervascular shell with a large hypovascular centre. Conventional HAG gives a false impression of a vascular tumour in such cases because it gives only a plain two-dimensional picture. The volume of the vascular spaces within these tumours is also relatively small, and it can retain very little of an injected therapeutic substance. These cases are not suitable for intrahepatic-arterial treatment.

The Tc^{99m}-MAA scan has been used to assess the vascularity of metastatic liver cancer and to predict the T/N ratio in SIR therapy [1, 2, 4–6]. The present study attempts to elucidate whether conventional HAG can give a good estimation of the tumour vascularity in HCC as compared with the Tc^{99m}-MAA scan.

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Patients and methods

A total of 51 patients with HCC (histologically proven or with α-fetoprotein elevated above 500 μg/l and ultrasonic evidence of a liver tumour) who were planned to undergo HAG as part of examinations

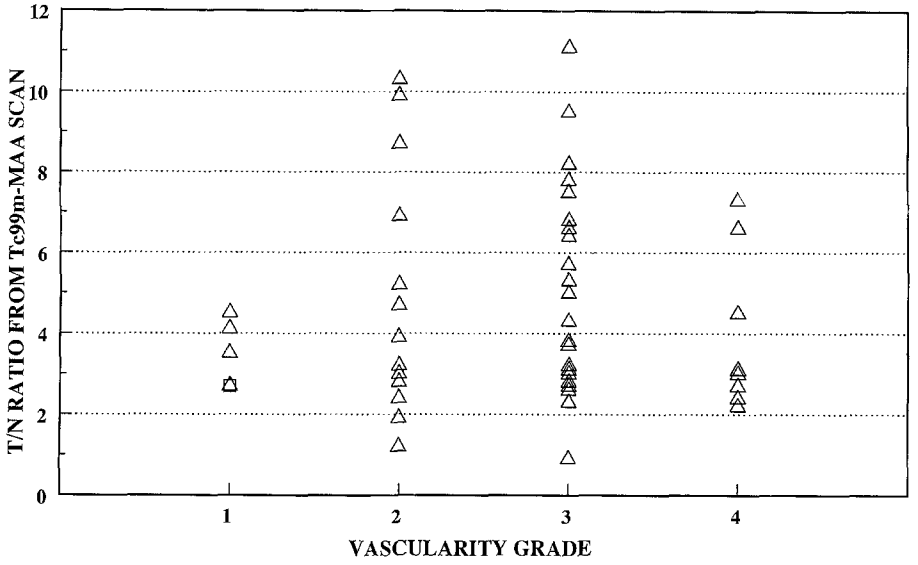

Fig. 1. Plot of T/N ratio against vascularity grades

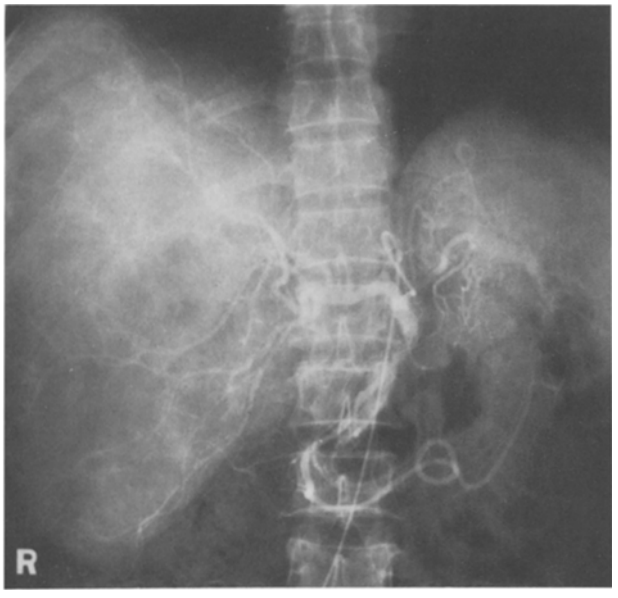

Fig. 2. HAG of grade/vascularity

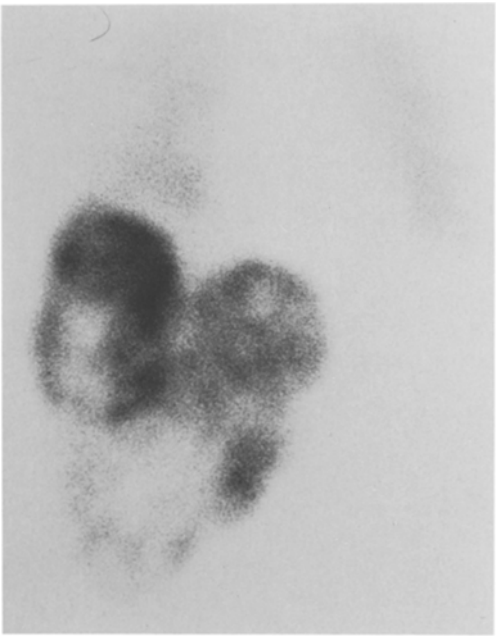

Fig. 3. Tc^{99m}-MAA scan, T/N ratio 3.5

Table 1. Vascularity grades and mean T/N ratio

Grade	No. of cases	Mean T/N ratio
1	5	3.5
2	13	4.9
3	24	4.9
4	9	3.8

were entered into the study. HAG was performed by the Seldinger technique. First, a diagnostic set of angiographic pictures was taken. With the angiographic catheter still in the hepatic artery, 111 MBq (3 mCi) of Tc^{99m}-MAA (Amersham Pulmonate II; with 80% of the particles having a size of 10–60 μm and none being greater than 150 μm) was injected into the hepatic artery following 20 μg of angiotensin II (Ciba). The catheter was then removed. The patient was then transported to the gamma-camera suite, and scintigraphic images of the liver were taken with an analog/digital gamma-camera (Philips).

The T/N ratio was calculated by quantifying the count rates over the tumours and the normal liver areas. The interventional radiologist who performed the HAG scored the vascularity on the HAG films using a scale ranging from 1 (hypovascular) to 4 (extremely hypervascular). The presence of mild tumour staining without any increase in the number of vessels was grade 1. Moderate tumour staining and an increased number of vessels was grade 2. Intense tumour staining and a markedly increased number of vessels, which were also dilated and tortuous, was grade 3. Tumours having all of the grade 3 characteristics that also showed venous pooling were classified as grade 4. The HAG vascularity grading was compared with the T/N ratio from the Tc^{99m}-MAA scan.

Results

The distribution of the different grades of vascularity were: 5 grade-1 cases, 13 grade-2 cases, 24 grade-3 cases and 9 grade-4 cases. The median T/N ratio from the Tc^{99m}-MAA scan was 3.7 (range, 0.9–11.1). Table 1 shows the vascu-

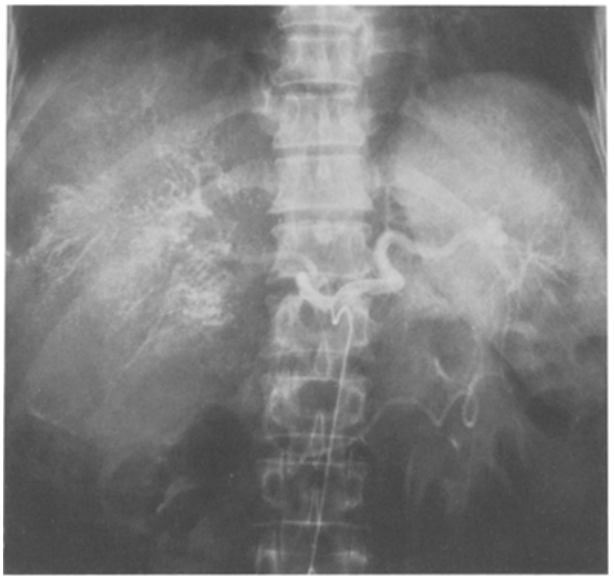

Fig. 4. HAG of grade 3 vascularity

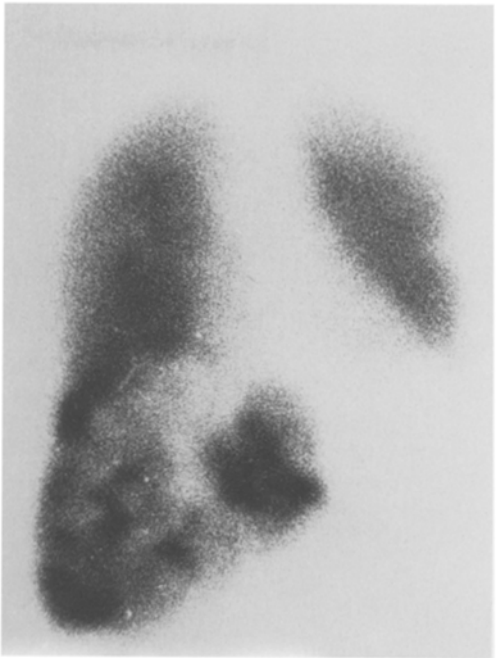

Fig. 5. Tc^{99m}-MAA scan, T/N ratio 0.9

larity grading and the mean T/N ratio, and Fig. 1 shows the distribution of the T/N ratio in relation to the vascularity grading. The T/N ratio of grade-1 and -2 tumours (slight to moderate increase in vascularity) was compared with that of grade-3 and -4 tumours (severe to extreme increase in vascularity), but there was no statistically significant difference between the two groups (Wilcoxon rank test, $P \approx 0.83$). Thus, the assessment of vascularity by HAG correlates poorly with the T/N ratio as assessed by Tc^{99m}-MAA scan.

Two cases are reported herein to illustrate the discrepancy. The first patient was diagnosed to have HCC by laparotomy and biopsy in another hospital. The surgical findings confirmed a relatively hypovascular tumour and

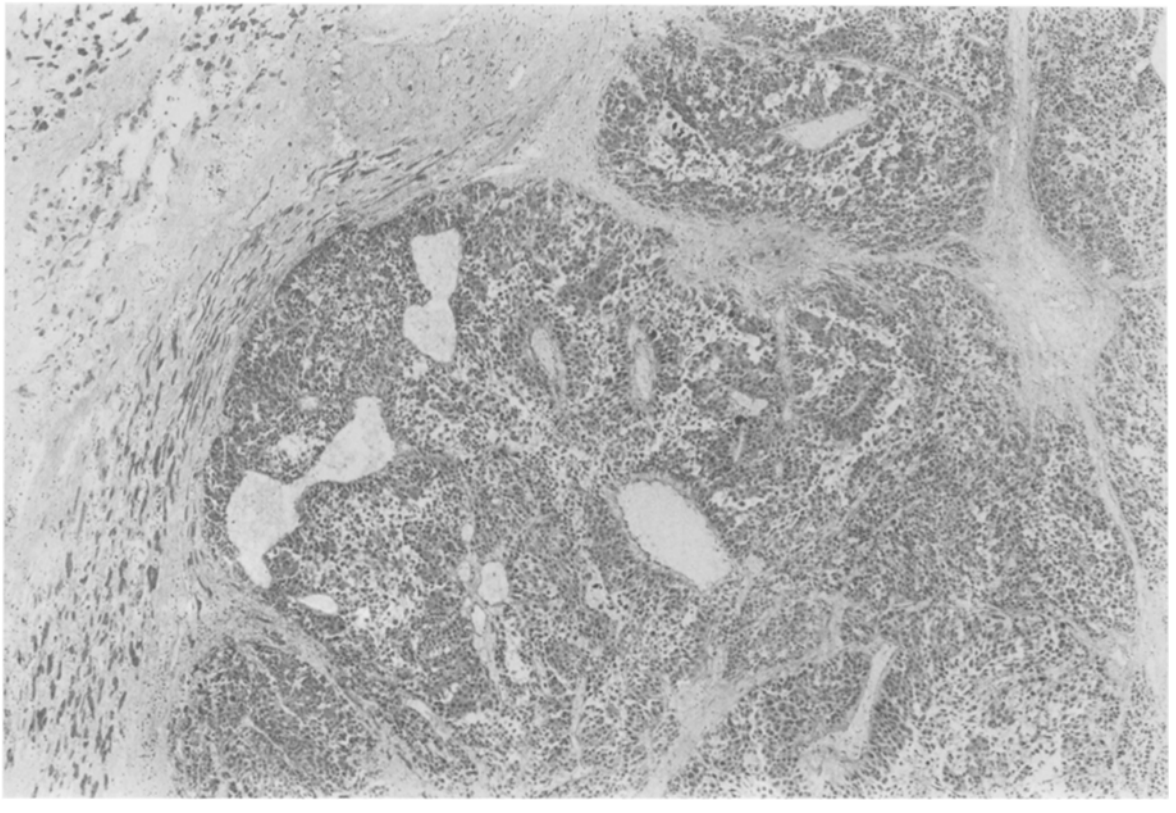

Fig. 6. Liver biopsy photomicrograph of the second patient

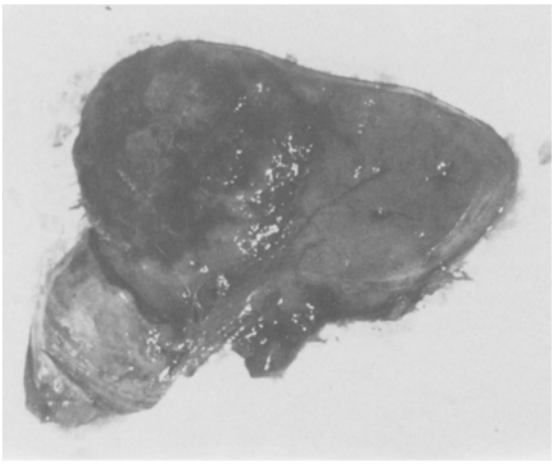

Fig. 7. Gross appearance of the tumour of the second patient

the HAG-assessed vascularity by our radiologist was grade 1 (Fig. 2). However, this case showed a good T/N ratio of 3.5 on the Tc^{99m}-MAA scan (Fig. 3). Conversely, in the second patient the HAG-assessed vascularity was grade 3 (Fig. 4), whereas the T/N ratio from the Tc^{99m}-MAA scan was only 0.9 (Fig. 5). The photomicrograph and the gross appearance of the tumour of the second patient are shown in Figs. 6 and 7, respectively.

Discussion

Locoregional intrahepatic-arterial chemotherapy, chemoembolisation and internal radiation therapy are increasingly used in the treatment of inoperable HCC. The success of treatment depends not just on the sensitivity of the tumour to the cytotoxic agents but also on the therapeutic advantage provided by the intrahepatic-arterial treatment. This advantage is dependent on the targeting efficiency of the injected substance (e.g. a mixture of Lipiodol and cytotoxic drugs, radiolabeled Lipiodol or microspheres). The more preferentially the agent accumulates in the tumour and the longer it stays within the tumour, the better will be the therapeutic efficacy. Because a lower dose is delivered to the normal cells, the toxicity is tolerable. The degree of preferential flow to the tumour is reflected in the T/N ratio. However, this issue is seldom addressed in various intrahepatic-arterial treatment programmes. The introduction of the Tc^{99m}-MAA scan has provided an accurate method for predicting the T/N ratio, and it is helpful in the selection of cases suited for intrahepatic-arterial treatment [1, 6].

Our study showed that HAG assessment of the vascularity correlated poorly with the T/N ratio as estimated by Tc^{99m}-MAA scan. HAG has limitations because it is only a two-dimensional assessment. It gives only a subjective assessment of vascularity and reflects the T/N ratio poorly. Sometimes the HAG results can be quite misleading. A tumour that has a thin hypervascular shell but a large necrotic centre can look very hypervascular on HAG. Such a tumour is obviously not suited for locoregional intrahepatic-arterial treatment.

Our study shows that the vascularity in HCC is very variable, and HAG was inaccurate in its estimation. We conclude that the Tc^{99m}-MAA scan is a better tool for the determination of tumour vascularity, and it also gives a quantitative measurement in terms of the T/N ratio. We recommend its use before intrahepatic-arterial treatment for HCC.

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