Quantification of Response of Hepatocellular Carcinoma(HCC) to Bevacizumab by Contrast Enhanced MRI

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Introduction:

Hepatocellular carcinoma accounts for over 400,000 deaths worldwide and 13,000 deaths in the United States per year[1]. Human HCC cell lines overexpress vascular endothelial growth factor (VEGF)[2]. Bevacizumab (formerly known as rhuMab-VEGF, commercial name Avastin) is a recombinant humanized version of a murine anti-human VEGF monoclonal antibody. This antibody binds all biologically active forms of VEGF-A (including VEGF165, VEGF121 and the thrombin-split fragment VEGF110). Bevacizumab has been shown to inhibit tumor growth in numerous animal models.

Materials and Methods:

Eight patients were analyzed. A pre-treatment MRI was performed on each patient between 3 and 13 days (mean 6 days) before the first dose of Bevacizumab. The administered dose was 5 or 10 mg/kg and continued at two-week intervals. A repeat MRI examination was planned at approximately 8 weeks (subsequent to 4 treatments). The MRI protocol utilized for this study was a routine liver protocol utilized at our institution performed on either a 1.5 Tesla General Electric (GE) Signa or Siemens Sonata machine. The data for this report was collected from the 3D spoiled gradient echo T1 weighted sequence performed after a timing bolus and repeated three times to visualize the arterial, portal-venous, and delayed venous phases of contrast enhancement. 0.2 mmol/kg gadolinium chelate (Magnevist; Berlex Laboratories, Wayne, NJ) was administered. The images were analyzed and whenever possible 'virgin' tumors were selected for followup. These included tumors, which did not receive prior chemo-embolization and/or radio frequency ablation. Similarly, tumors demonstrating necrosis were avoided. Regions of interest (ROIs) were drawn on a non-necrotic portion of the tumor and a mean value of the signal intensity (SI) was recorded. In addition, a second ROI was placed in the normal liver parenchyma. This was chosen in a region closest to the tumor but devoid of vessels and artifacts. The vertical distance from the coils was preserved in both ROIs so as to avoid near-field artifact. The above steps were repeated for both the arterial and portal-venous phase of each of the patient's examination. Values were calculated using the following equation: $(SI_{lesion}-SI_{normal})/SD_{air}$[3]. A total of 22 lesions were analyzed from 8 patients. The longest diameter of the lesion was selected for follow-up. Lesions, which could not be visualized on the post treatment examination, were excluded from the study. All values were averaged per patient to avoid inadvertently biasing the data in favor of the patients with more detectable lesions.

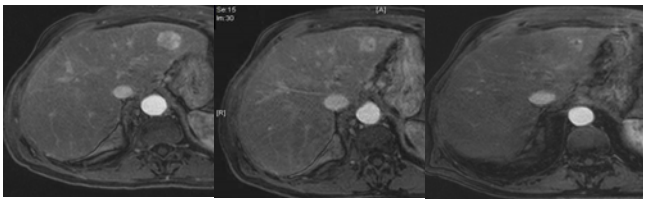
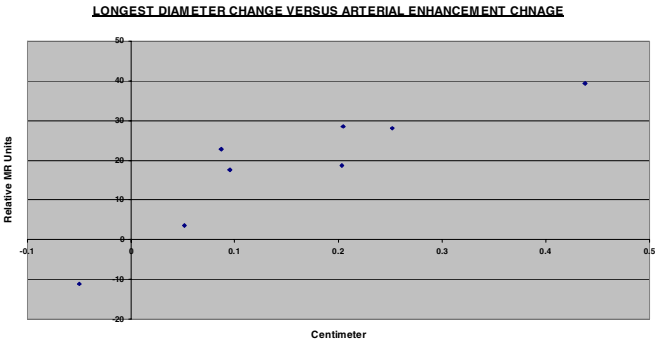


Figure: Demonstrating sample lesion at base line, 8 and 16 weeks of therapy with good response.



Results:

A reduction of arterial enhancement was seen in 7 out of 8 patients which was statistically significant($p=0.023$ Wilcoxon signed-rank test). The average tumor size in the patients was 1.72 cm before therapy and 1.43 cm after therapy. The mean reduction in tumor size following therapy is 0.16 (median 0.15) with a SD of 0.15. The reduction in tumor size was statistically significant($p= 0.016$, Wilcoxon Signed rank test). There was a correlation between arterial enhancement change and size change($r=0.90$ Spearman, $p<0.01$) in all eight patients including the patient who did not demonstrate a decreased enhancement.

Discussion:

The study demonstrated that anti-angiogenic therapy can be monitored by contrast enhanced MRI protocols in routine practice as demonstrated by the good correlation in all patients. The results demonstrated a high variability between patients in their MR response to Bevacizumab but the good correlation between signal intensity change and change in tumor size may have potential implication for patient selection in the future. As alluded to by a hallmark study by Morgan et al.[4] high temporal resolution is not necessarily important when there is high response of tumor to the medication under investigation.

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