

Ultrasound imaging provides noninvasive 3D views into vascular changes in response to cancer therapy.

Assessing therapeutic response in renal cell carcinoma

Monitoring tumor response to therapy is a fundamental part of oncology drug assessment and screening. Typically, tumor response is assessed by measuring morphological changes in tumor volume using the RECIST (Response Evaluation Criteria in Solid Tumors) guidelines, a widely accepted criteria for clinical evaluation of response to therapy. However, functional and molecular changes, such as reductions in vascular density, occur before any measurable change in tumor size. This suggests that a more efficient way to assess and predict therapeutic response would be to measure these earlier changes in the clinic.

In a recent study, researchers explored whether ultrasound microvascular imaging might provide indications of treatment response earlier than changes in tumor volume in a mouse model of renal cell carcinoma.¹ The imaging system used for the work was a Vega® platform, which allows for automated 3D ultrasound image acquisition from mice. Ultrasound is portable, inexpensive, fast, and is free of ionizing radiation, making it an attractive imaging approach compared to MRI, CT, or PET.

Broader applications of ultrasound microvascular imaging

- Understanding vascular supply to tumors over time in conjunction with cell therapy approaches
- Better inter-group randomization in oncology studies as effects of heterogeneous tumor perfusion can be accounted for, reducing downstream error bars that might mask therapeutic effects
- Rapid assessment of the temporal dynamics of wound healing and other physiological processes driven by vascular infiltration, such as those within implantable biomaterials

Methods and results

Mice bearing clear-cell renal cell carcinoma xenograft tumors were treated with either an antiangiogenic therapy (Sunitinib malate; SU), a combination of antiangiogenic and Notch inhibition therapies (combo), or saline (control) for four weeks once their tumors reached a size of 200 mm³. For imaging, VesselVue[®] microbubble contrast agents (MCAs) were infused into the tail vein of the mice and images were captured once a week. A measurement of microvascular density was used to assess the tumor response to therapy. Figure 1 shows blood vessel density images for each treatment group before the start of treatment and at the end of the study.

One of the key study findings was that ultrasound measures of vascular density detected tumor response to therapy a week earlier than tumor volume. For example, it took just one week of treatment for the blood vessel density in both

treatment groups to be significantly lower than the controls, whereas it took two weeks for tumor volume to become significantly different between the groups (Figure 2). While a week may not seem that substantial, the authors note that the difference of a week in mice may translate to greater timescales in humans.

The findings also demonstrate that ultrasound measurements of vascular density can be used to predict treatment response from around day seven with a high degree of confidence before tumor volume measurements become significantly different. They can also classify between-treatment groups with high sensitivity and specificity. The team also confirmed that image-based vascular density strongly correlated with the physiological characteristics of the tumors measured by histology.

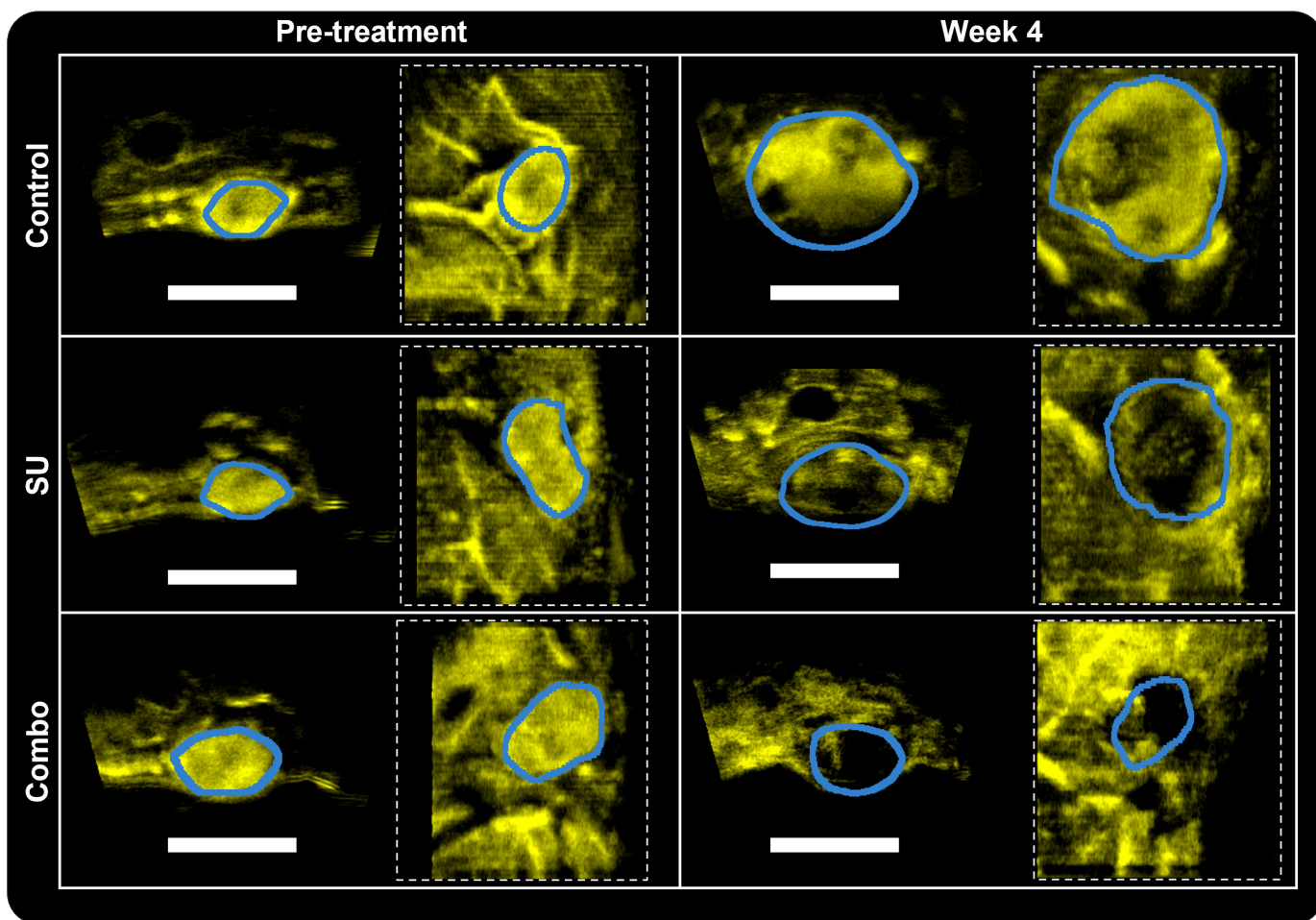


Figure 1: Representative vessel density images from the different treatment groups. Representative images are displayed at the beginning (left) and end (right) of the study. In each panel, the image on the left is a cross-section of the tumors while the image on the right (dashed square) is a coronal view. The scale bar represents 1 cm. Yellow indicates microvasculature acquired in acoustic angiography mode. The blue outlines the tumor region of interest and was derived via registered anatomical B-mode images (not shown). Image credit: Rojas et al. 2019

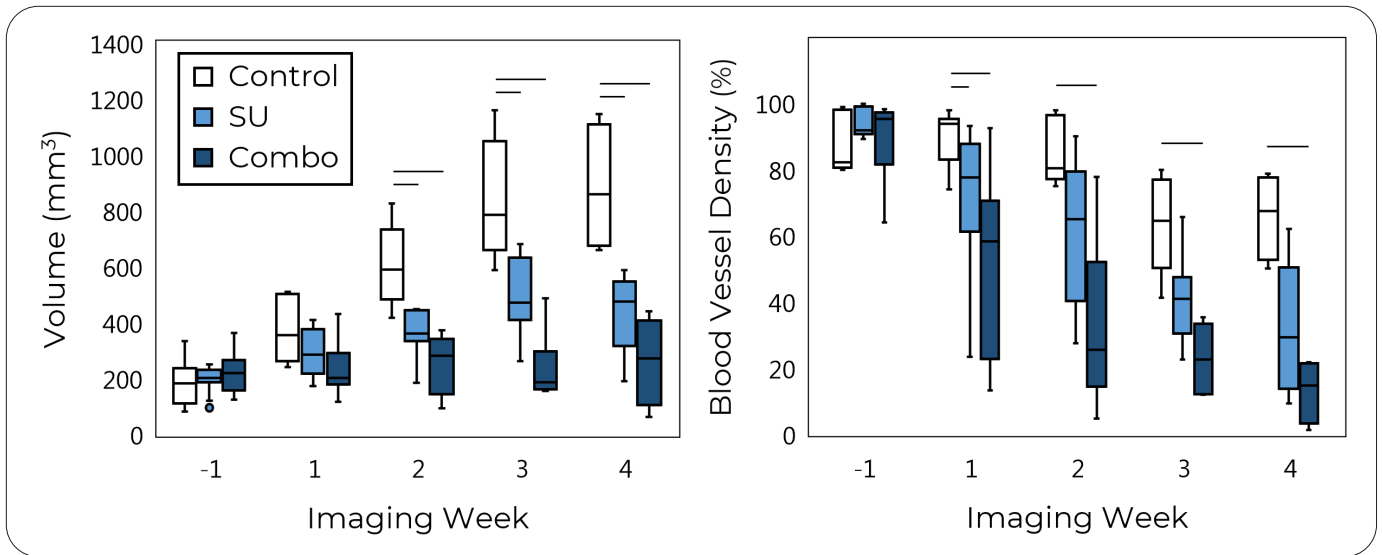


Figure 2: Tumor volume and blood vessel density for the different imaging weeks. The vessel density (right) of the SU and Combo groups became significant ($p < 0.05$) from the Controls one week after the start of treatment, while it took two weeks for a significant difference in volume (left) to emerge. Significance is denoted by the horizontal bars. Image credit: Rojas et al. 2019

Conclusion

Conventional methods for evaluating response to therapy typically rely on changes in tumor volume; however, assessing tumor volume has been shown to be inaccurate and often underreports the effect of therapy. Imaging approaches, such as MRI and PET, have been shown to be effective at predicting response to therapy, but high costs, long imaging times, and radiation risks have limited their clinical application.

In this study, researchers demonstrated that an ultrasound measure of vascular density can be used to assess the response of renal cell carcinoma tumors to antiangiogenic and Notch inhibition therapies earlier than the clinical gold standard of tumor volume. These results suggest that using ultrasound microvascular imaging may provide earlier insight into tumor behavior than current approaches.

Reference

1. Rojas JD, Papadopoulou V, Czernuszewicz TJ, Rajamahendiran RM, Chytil A, Chiang Y-C, et al. Ultrasound measurement of vascular density to evaluate response to anti-angiogenic therapy in renal cell carcinoma. *IEEE Transactions on Biomedical Engineering*. 2019;66(3):873–80.

For research use only. Not for use in diagnostic procedures.

revvity