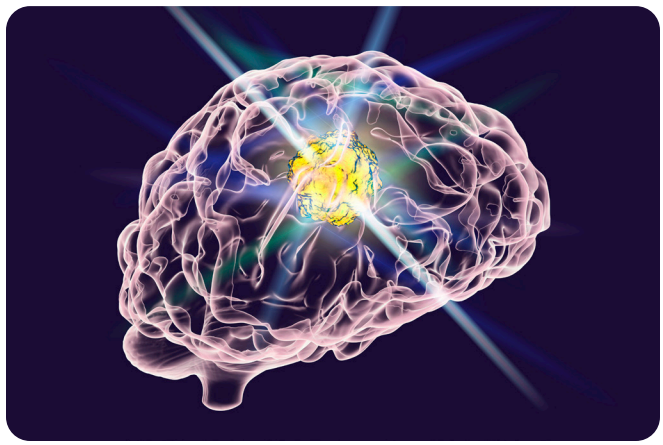
CASE STUDY

Assessing murine glioblastoma growth: a comparative study of ultrasound and MRI imaging modalities

Glioblastoma (GBM) is the most common and aggressive form of primary brain tumor, known for its rapid progression and resistance to conventional therapies. With fewer than 5% of patients surviving longer than five years post-diagnosis, there is an urgent need for novel therapeutics targeting this deadly disease.

Murine models of GBM are valuable tools in preclinical studies, offering a platform to advance our understanding of tumor biology and evaluate emerging therapeutics. However, the utility of these models relies on the ability to accurately track tumor progression over time—a task which has proven to be extremely challenging. Traditional monitoring techniques involve invasive and time-consuming methods, while noninvasive small animal MRI, despite its sensitivity, is hindered by its high costs and operational demands.

Despite its historical limitations, such as poor skull penetration and low contrast, recent advances in ultrasound technology have positioned this modality as a cost-effective and high-throughput alternative to MRI as a brain imaging modality in mice. This was demonstrated in a recent collaborative study where researchers from Revvity, UNC-Chapel Hill, and NC State University evaluated a 3D contrast-enhanced ultrasound imaging technique adapted to rapidly measure tumor volumes *in vivo* in murine models of GBM. Using the Vega™ ultrasound system's acoustic angiography (AA) mode—a proprietary contrast enhanced ultrasound (CEUS) imaging mode—along with VesselVue™



microbubble contrast agent, the researchers demonstrated a correlation with MRI-derived tumor volume measurements, highlighting its potential as an alternative tool for real-time GBM monitoring in mice.

Study design

In this investigation, six-week old female athymic nude mice (n=16) were implanted with U87 GBM cells in the brain. The mice were imaged using both MRI and the Vega ultrasound system twice a week for four weeks, starting one week post-implantation. The ultrasound imaging process was facilitated by the administration of injectable VesselVue contrast agents, which were used to visualize the microvasculature of the brain. Figure 1 illustrates the image acquisition approach used for ultrasound imaging.

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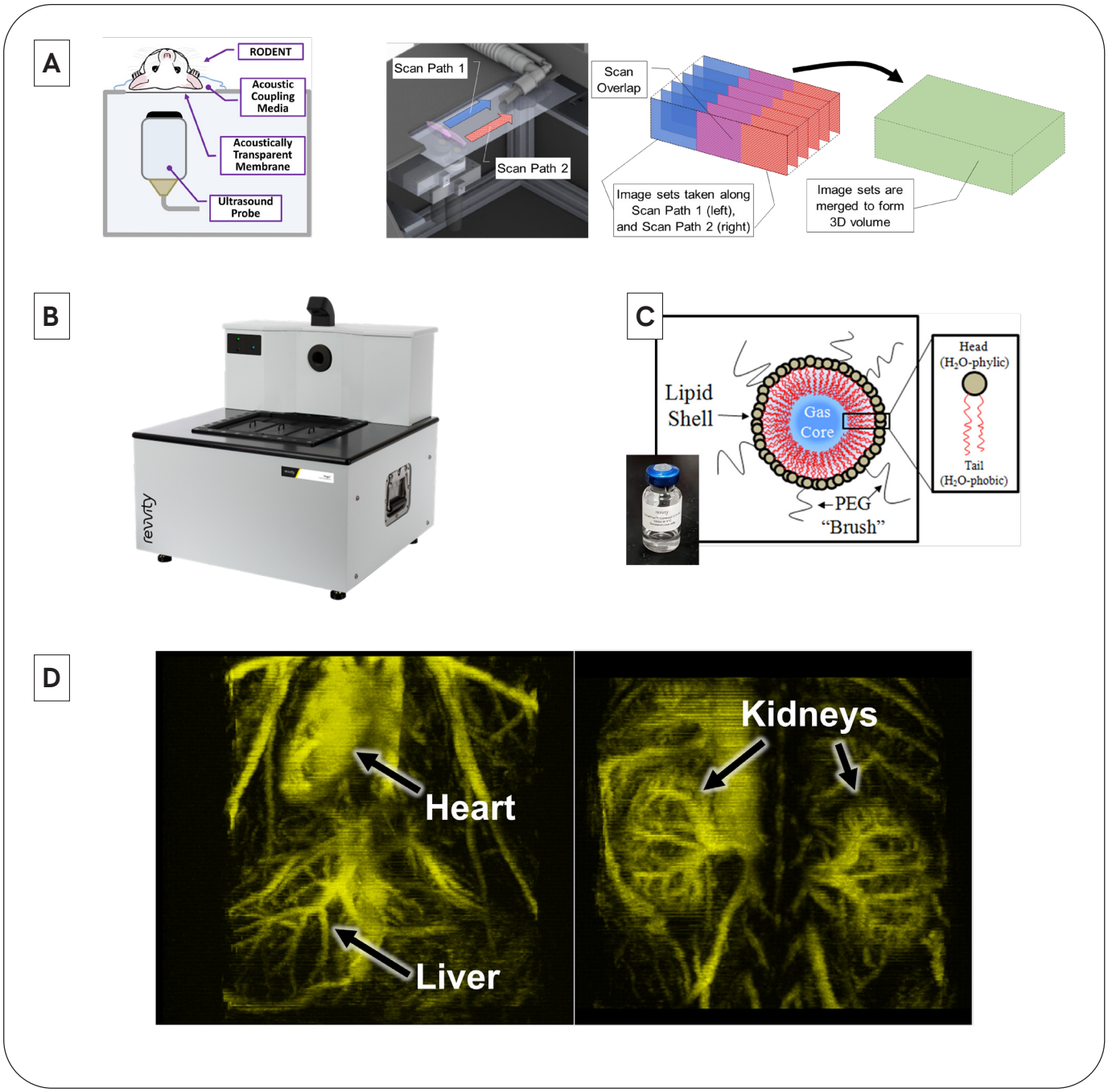

Figure 1: Schematic overview of image acquisition approach using the Vega imaging system. A: How the bottom-up approach captures widefield images of rodents. **B:** Photo of Vega imaging system. **C:** Illustration of VesselVue microbubble ultrasound contrast agent. **D:** *In vivo* 3D acoustic angiography data in a mouse liver (left) and kidneys (right).

Study findings

When the researchers compared GBM tumor growth using both ultrasound and MRI (Figure 2), they observed that ultrasound imaging with the Vega system detected tumors 3 mm in diameter and larger with sensitivity that matched that of MRI. As shown in Figure 3, ultrasound detected 72.2% (26 out of 36) of tumors visible on MRI, with a 100% detection rate for tumors greater than 3 mm in diameter.

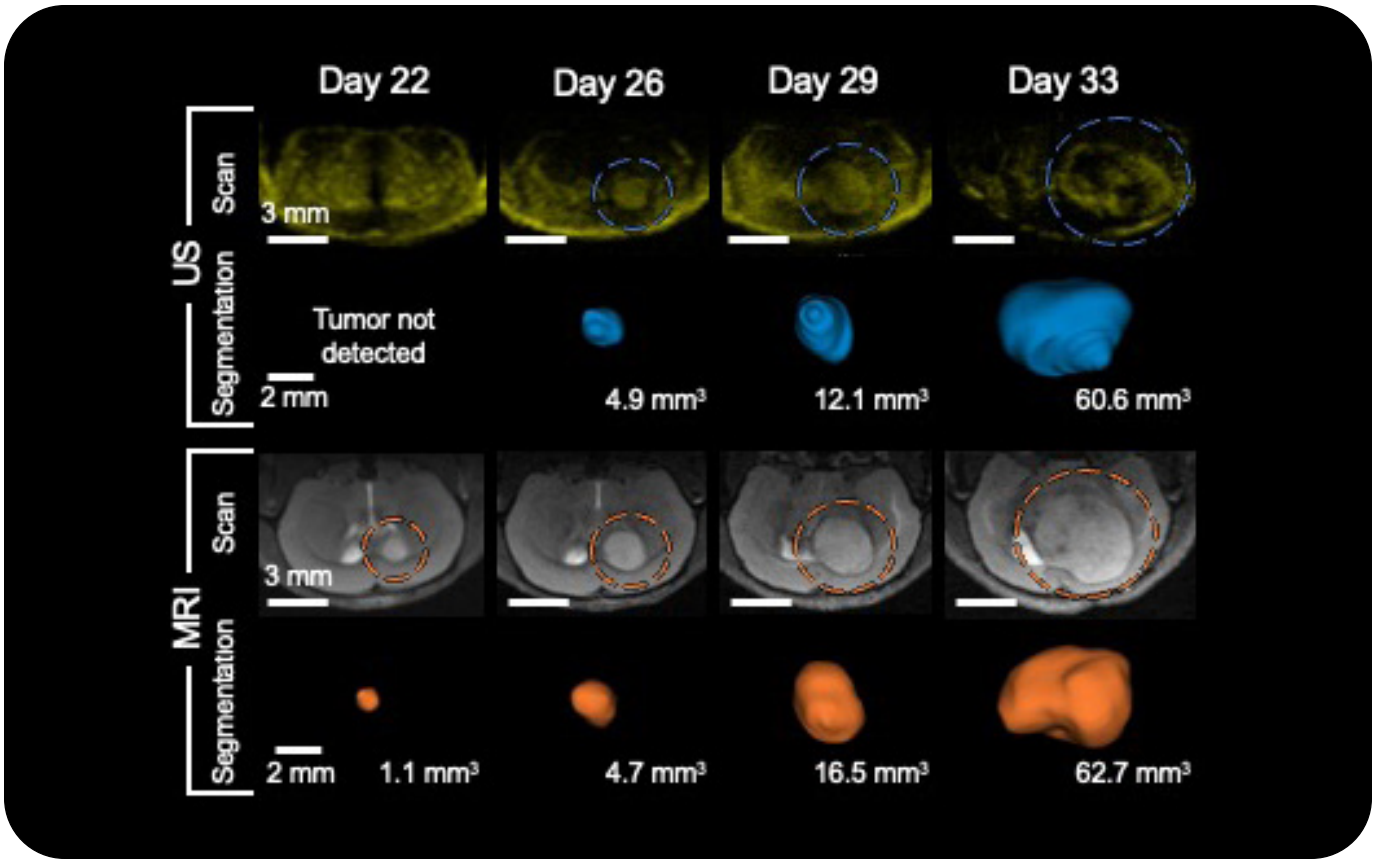

Figure 2: Representative tumor growth images. Representative tumor growth images of ultrasound (top row) and MRI (third row). The 3D rendering of the segmentations are shown in rows 2 and 4 for ultrasound and MRI, respectively. Tumor location is indicated by the dotted circles.

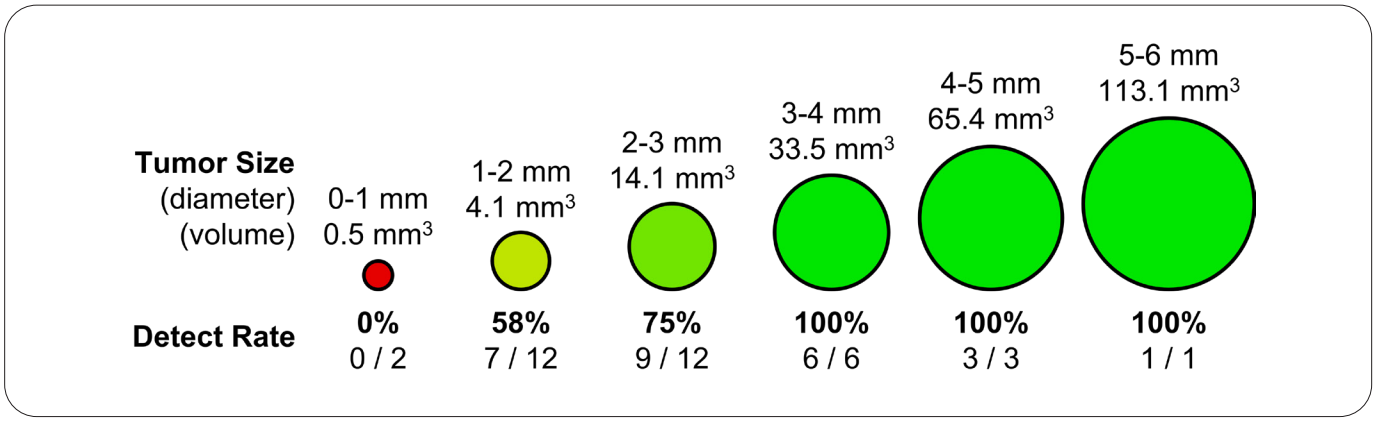

Figure 3: Ultrasound detected 72.2% (26 out of 36) of the tumors that were seen in MRI. The mean volume, as measured by MRI, of tumors that were missed by ultrasound was 2.3 mm^3, while the mean volume of tumors that were detected by ultrasound was 8.0 mm^3. Smaller tumors were more easily detected in ultrasound images in areas of the brain with lower surrounding AA signal, suggesting higher difference in vascular density between diseased and healthy brain tissue.

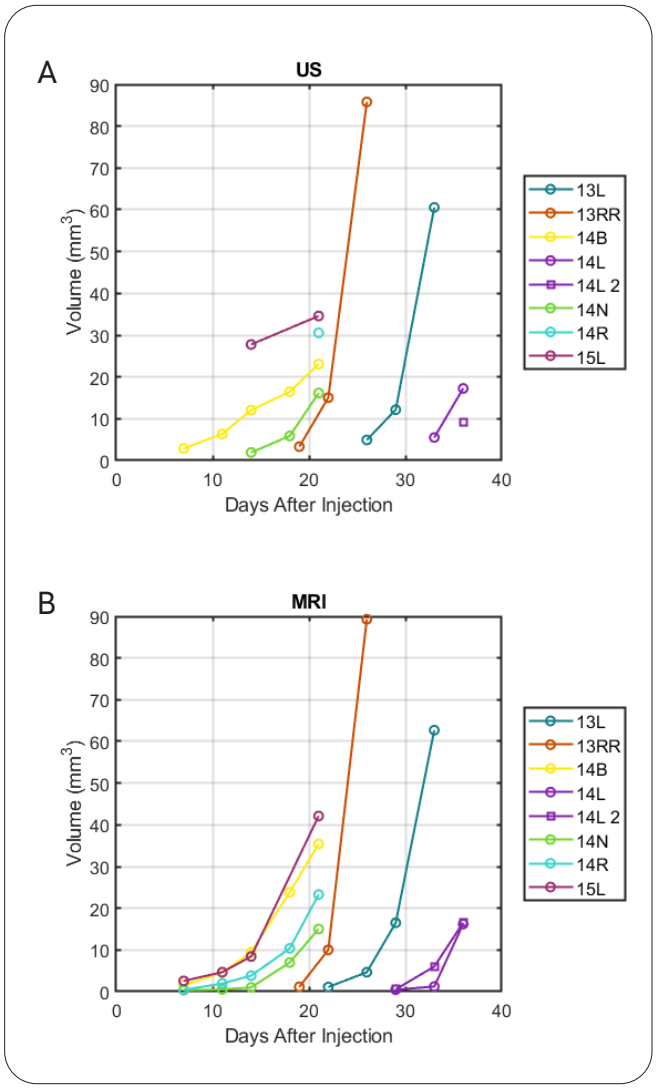

Figure 4: Longitudinal growth curves. Tumor volume over time for ultrasound (A) and MRI (B). The growth curves measured by ultrasound and MRI are similar for tumors that ultrasound detected in multiple timepoints.

Notably, once a tumor was detected by ultrasound, its growth curve tracked similarly to MRI (Figure 4). Although ultrasound did not detect as many small tumors as MRI, there was a strong correlation (R^2 = 0.92) between the volume measurements obtained by both modalities for the detected tumors, as shown in Figure 5. This confirms that, while ultrasound may miss some tumors in the 0-3 mm range, the volume measurements it provides for the tumors it does detect are consistent with those obtained by MRI.

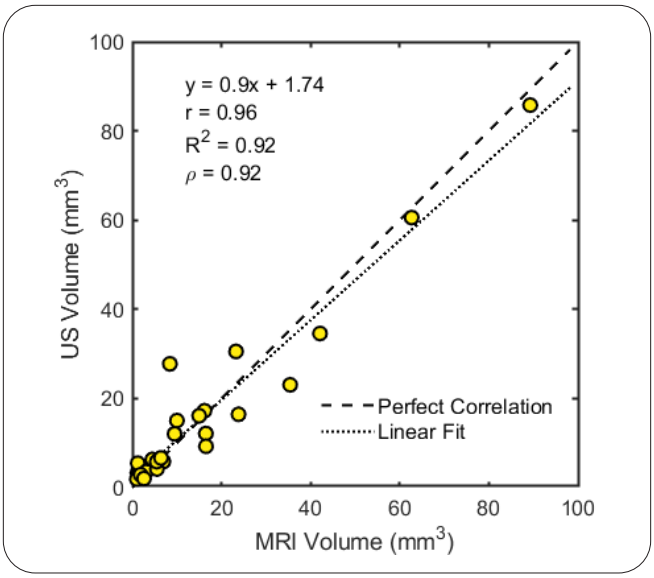

Figure 5: Correlation plot of ultrasound vs MRI volume measurements. R=Pearson correlation coefficient, R^2=coefficient of determination, ρ=Spearman correlation coefficient.

Conclusion

These findings demonstrate the potential of ultrasound imaging using the Vega system as a complementary imaging tool to MRI for assessing GBM in mice. Ultrasound shows comparable sensitivity to MRI for tumors measuring larger than 3 mm and can effectively monitor tumor growth over time, providing equivalent volume measurements to those obtained using MRI. Additionally, using AA mode and VesselVue reagents, ultrasound can visualize vasculature, a capability traditionally limited to MRI.

These results highlight the potential of ultrasound imaging for tracking tumor progression, particularly in later stages when tumors are more easily detectable. Furthermore, these findings suggest that the Vega system could be used in drug discovery research to prioritize compounds for further evaluation before committing to MRI, which is more time-consuming and expensive. Future work will aim to optimize ultrasound imaging parameters to enhance sensitivity and broaden its applicability in detecting smaller tumors.

Key takeaways

- The Vega ultrasound system, when used with VesselVue microbubble contrast agent, has demonstrated its potential as a complementary imaging tool to MRI for assessing GBM in mice.
- Ultrasound with the Vega system shows comparable sensitivity to MRI for detecting GBM tumors larger than 3 mm in diameter, making it an attractive modality for tracking tumor progression as they grow larger.
- There is a strong correlation between the volume measurements of tumors obtained by ultrasound and MRI, confirming the accuracy of ultrasound in providing consistent volume metrics.
- Utilizing AA mode and VesselVue reagents, the Vega system can non-invasively visualize vasculature in the brain, a capability traditionally limited to MRI, enhancing the overall capability of ultrasound.
- The higher throughput of the Vega ultrasound system compared to MRI makes it an attractive approach for reducing study time or conducting large cohort studies.

Reference

Kierski, T. M., Rojas, J. D., Durham, P. G., Dayton, P. A., Thang, M., Hingtgen, S. D., Czernuszewicz, T. J., & Gessner, R. C. (2024). Noninvasive measurement of murine glioblastoma *in vivo* with a benchtop ultrasound instrument [Poster presentation]. Presented at AACR. San Diego, CA.

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