

# From Vibrational Spectroscopy to Whole-Body Imaging: Multimodal Strategies for Cancer Imaging and Monitoring

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## **Abstract**

Achieving high molecular selectivity and specificity for deep tumor detection remains a major challenge in optical imaging. Surface-enhanced resonance Raman scattering (SERRS) nanoparticles provide exceptional sensitivity as contrast agents; however, conventional Raman spectroscopy is limited by shallow tissue penetration (typically only a few millimeters) and slow point-by-point acquisition. To overcome these barriers, we integrate spatially offset Raman spectroscopy (SORS) with SERRS in surface-enhanced spatially offset resonance Raman spectroscopy (SESORRS). Using SESORRS, we achieve rapid, non-invasive molecular imaging of deep-seated tumors, including the detection of glioblastoma through the intact skull, validated by MRI and H&E staining, and demonstrate further applicability in colorectal cancer models using tissue phantoms and orthotopic tumors. In parallel, we optimize SERRS nanoparticle synthesis and surface chemistry to improve optical properties, targeting specificity, *in vitro* and *in vivo* stability, and show that the performance of silica-encapsulated gold nanostars is governed by subpopulation heterogeneity and silica nanoshell degradation, with near-neutral physiological conditions altering intracellular SERRS intensity. Finally, we demonstrate the use of vibrational spectroscopy to assess therapy-induced DNA damage following treatment with external beam radiation and/or radioligand therapy, in agreement with immunofluorescence, highlighting opportunities for multimodal imaging, image-guided intervention, and longitudinal tumor monitoring.