New theranostic approach reduces tumor volume and increases survival in NET study

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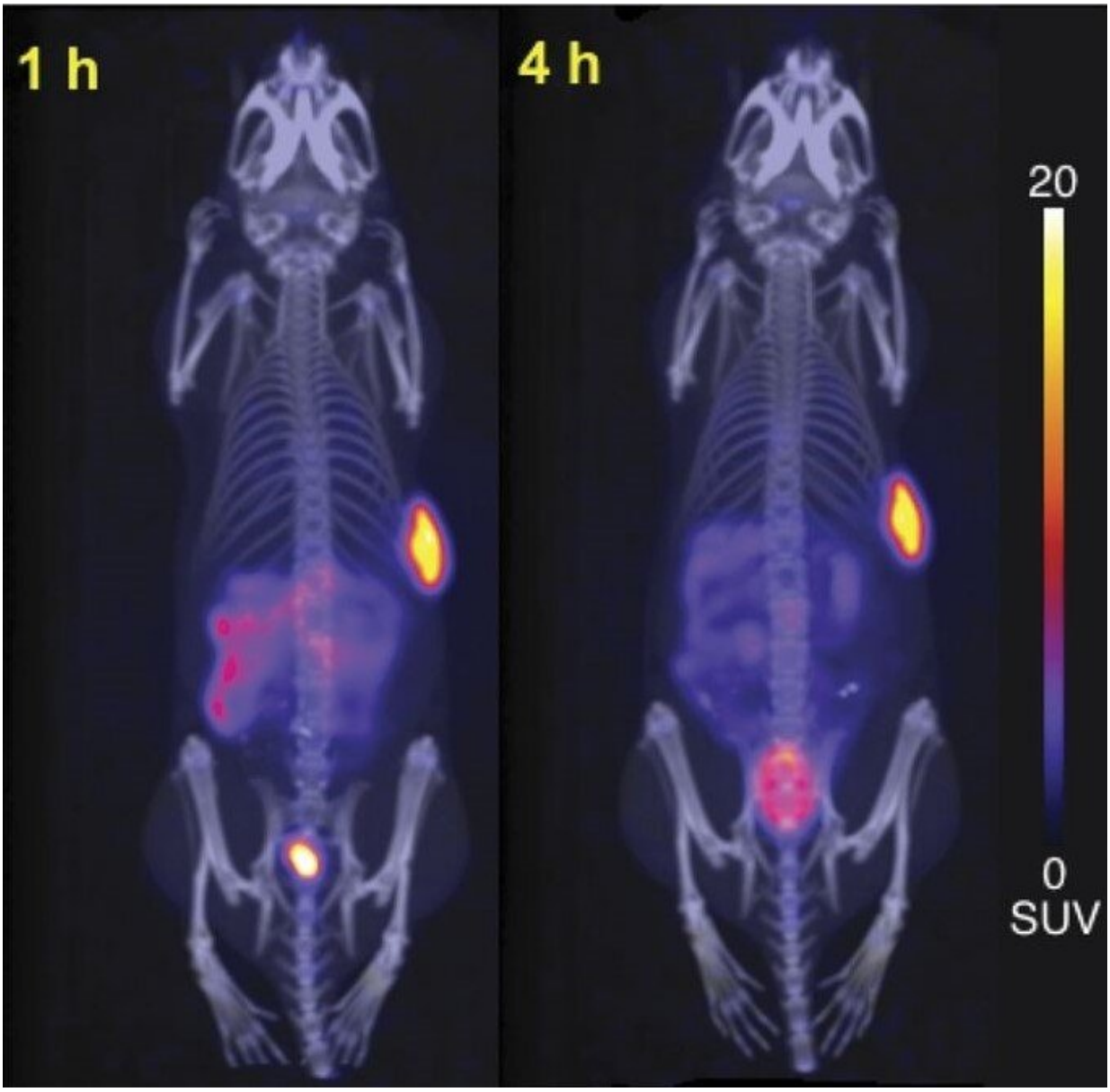

Representative maximum intensity projection PET/CT images of AR42J tumor-bearing female Balb/c nude mice following injection of ^{64}Cu-CuSarTATE (3 MBq, 0.24 nmol of peptide) at 1 and 4 hours post injection. Credit: Society of Nuclear Medicine and Molecular Imaging

A pair of copper radionuclides that target the somatostatin receptor overexpressed in neuroendocrine tumors has proven successful in identifying tumors and improving survival. According to new research published in the December issue of *The Journal of Nuclear Medicine*, the imaging agent ^{64}Cu-CuSarTate produced high-quality positron emission tomography (PET) images in a mouse model of neuroendocrine tumors, while its therapeutic counterpart, ^{67}Cu-CuSarTate, was highly effective in reducing tumor volume and extending lifespan. The research also demonstrated the advantages of delivering the radionuclide therapy as two fractionated doses, as opposed to one.

Neuroendocrine tumors typically are diagnosed with ^{68}Ga-DOTA-octreotate and treated with ^{177}Lu-LuTATE peptide receptor radionuclide therapy. However, using two different chemical elements (Ga and Lu) can lead to inconsistent tissue biodistribution, as they do not have the same binding and internalizations interactions. "Ideally, a chemically identical 'imaging-therapeutic' pair of radionuclides bound to the same targeting agent should be used for diagnosis and treatment," said Paul S. Donnelly, BSc(Hons), Ph.D., professor in the School of Chemistry at the University of Melbourne in Melbourne, Victoria, Australia.

In the study, researchers utilized a preclinical mouse model to explore the chemically identical radionuclide pair ^{64}Cu-CuSarTate and ^{67}Cu-CuSarTate. To assess the ability of ^{64}Cu-CuSarTate to positively identify tumors, PET imaging occurred at one hour and four hours after injection of the radiotracer. On completion of the four-hour imaging, mice were

euthanized and biodistribution studies were performed.

Multiple therapy experiments were also performed to evaluate the efficacy of ^{67}Cu-CuSarTate. In the first, mice were injected with five MBq of ^{177}Lu-LuTATE, five MBq of ^{67}Cu-CuSarTate or saline and monitored for tumor growth. In the second experiment, mice were injected with a total of 30 MBq of ^{177}Lu-LuTATE, ^{67}Cu-CuSarTate or saline either as a single intravenous injection or as two 15 MBq fractions, two weeks apart; tumor growth was then monitored.

^{64}Cu-CuSarTate PET images acquired at both one hour and four hours post-injection revealed very high tumor uptake and excellent tumor-to-background ratios. The high tumor uptake was confirmed with the ex vivo biodistribution analysis. Tumor growth was inhibited by 75 percent with ^{67}Cu-CuSarTate treatment and by 89 percent with ^{177}Lu-LuTATE, and survival was extended from 12 days in the control group to 21 days following treatment with both therapies. Treatment of tumors with two fractions of either ^{177}Lu-LuTATE or ^{67}Cu-CuSarTate significantly improved survival when compared to delivery as a single fraction. Equivalent efficacy was observed between the two therapies following treatment on both the single and fractionated schedules.

"Copper radionuclides are beneficial for several reasons," said Rodney J. Hicks, MBBS, MD, FRACP, FAHMS, professor in the Sir Peter MacCallum department of oncology at the University of Melbourne, in Melbourne, Victoria, Australia. "The strong binding of copper within the tumor allows for increased detection of disease, which can serve to limit radiation exposure to normal tissues during therapy. The ability to image at multiple time points with ^{64}Cu-CuSarTate supports prospective dosimetry for therapeutic treatment planning with ^{67}Cu-CuSarTATE, which could potentially offer shorter cycling of treatment, particularly for more aggressively growing tumors."

In terms of potential translation of the copper-^{64}/^{67} theranostic pair to clinical studies, it is pertinent that copper-^{64} is produced in a cyclotron. The longer half-life of ^{64}Cu-CuSarTATE as compared to 68Ga-DOTA-octreotate means that the tracer can be easily produced under good manufacturing practice conditions and transported regionally. ^{67}Cu-CuSarTATE can be produced with linear-accelerators in high specific activity and radionuclide purity, so it is not reliant on nuclear reactors.

"Looking to the future of molecular imaging and nuclear medicine, the chemistry and general concepts presented in this study could be expanded to other peptides that target different receptors, as well as antibodies and engineered antibody fragments. This offers the potential to provide diagnostic imaging using copper-^{64} to plan individualized treatments with copper-^{67} agents for a wide range of cancer patients," noted Donnelly.

More information: Carleen Cullinane et al, Peptide Receptor Radionuclide Therapy with 67Cu-CuSarTATE Is Highly Efficacious Against a Somatostatin-Positive Neuroendocrine Tumor Model, *Journal of Nuclear Medicine* (2020). DOI: 10.2967/jnumed.120.243543

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