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Smaller agents for larger therapeutic indices: nanoscale brachytherapy with ^{177}Lu-labeled gold nanoparticles

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It is estimated that over 240,000 cases of breast cancer will be diagnosed in the United States this year ([1]). Locally advanced breast cancer (LABC) is found in women with stage II or III cancers, and is generally characterized with a poorer prognosis than tumors diagnosed in earlier stages. Current standard-of-care treatments for LABC include neoadjuvant chemotherapy, hormonal therapy, and surgery ([2]). The use of neoadjuvant treatments may, in some instances, reduce the primary tumor size such that breast conserving surgery may be a viable option over a full mastectomy, thereby greatly improving the quality of life for these breast cancer patients.

In this issue of *the Journal of Nuclear Medicine*, Yook *et al.* presented a novel neoadjuvant treatment for LABC, involving the use of intratumorally (i.t.) injected gold nanoparticles (AuNPs) labeled with the radiotherapeutic isotope, ^{177}Lu ($t_{1/2}$: 6.7 days; E_{max}: 498 keV) ([3]). Utilizing mice with human breast cancer MDA-MB-468 xenografts, the authors described the effects of localized internal radiotherapy on the inhibition of tumor growth. ^{177}Lu-labeled AuNPs targeted to the epidermal growth factor receptor (EGFR) using panitumumab, as well as the same constructs without active targeting, were employed. In both cases, complete survival of the mice out to 120 days was observed. Emboldened by these results, the authors described a theoretical treatment plan for LABC patients using these agents that may enable a pathological complete response (pCR).

Brachytherapy (BRT) has found applications in breast cancer as part of post-surgery partial breast irradiation for lumpectomy patients ([4]), rather than the pre-operative use proposed in this study. It has been shown that recurrence of breast cancer most often occurs near the previously resected area, indicating microscopic tumor growth that was not removed ([5]). Thus, the use of a radiotherapeutic treatment in and around the lumpectomy bed is thought to help eliminate some of the infiltrating disease. External beam treatments, either using photon radiation post-surgery or electrons intraoperatively, have formed the backbone of these treatments traditionally ([6]). However, with improvements in BRT techniques, the highly localized dose profiles of these agents have recently found applications in breast

cancer patient management. Whether the ^{177}Lu-AuNPs in this study qualify as BRT agents, in the conventional sense of the word, is up for debate. While standard BRT agents utilize a solid encapsulation of radioisotopes such as ^{192}Ir ($t_{1/2}$: 74 days; E_{ave}: 0.38 MeV), ^{125}I ($t_{1/2}$: 59.4 days; E_{ave}: 0.028 MeV), and ^{90}Y ($t_{1/2}$: 64.1 h; E_{max}: 2.28 MeV) with sizes on the order of a centimeter, the agents in this study are approximately 30 nm in diameter and conjugated with ^{177}Lu ([7]). Traditional BRT agents are placed in the tumor volume using a catheter, while these ^{177}Lu-AuNPs were injected i.t. in saline.

I.t. injections have been utilized in a number of clinical trials in oncology ([8–10]), often with gene therapy and viral agents. However, internal radiotherapy with i.t. injected agents has not seen much clinical translation. Often, radiosensitizers may be injected i.t. and combined with external beam radiotherapy. Similarly, AuNPs are often used to sensitize tissues to radiation ([11]), rather than to provide a vehicle for the radiation itself, as investigated in this study. The i.t. injection technique used here helps to alleviate the normal tissue toxicity concerns that are found with many inorganic nanoparticles when administered intravenously, as they often accumulate in the liver and spleen ([12, 13]). In addition, the lower normal tissue uptake found here increases the therapeutic index of these treatments significantly over traditional internal radiotherapy treatments.

While the use of an i.t. technique certainly relieves concerns about normal tissue toxicity, the treatment itself may also suffer from the resulting heterogeneous distribution in the tumor. This has been one of the downfalls of standard BRT, and further investigation on the impacts of such heterogeneity is warranted ([14]). In this study, the ^{177}Lu-AuNPs obviously exhibit some diffusivity, evidenced by the accumulation in other normal tissue. However, more detailed evaluation of the distribution in the tumor itself is needed before future clinical translation. As this is a preclinical study, the tumor volumes found here are much smaller than those that would be found in a clinical case. Thus, the impact caused by heterogeneity would only increase in potential clinical studies. The use of ^{177}Lu, with an approximately 2 mm beta range, will smoothen the dose distribution to a certain extent. However, in the case of LABC, tumor diameters of at least 5 cm will certainly require more than one injection of the agent. Perhaps the conjugation of AuNPs with other radioisotopes (such as ^{90}Y, maximum beta range 1.1 cm) will reduce the heterogeneity of radiation dose delivered in larger tumor volumes.

One initially unexpected finding of this study is the similar performance of targeted (using panitumumab to target EGFR) and non-targeted ^{177}Lu-labeled AuNPs. Both agents led to complete survival of treated mice out to the 120-day endpoint of the study, with similar absorbed doses to the tumor (approximately 30 Gy for targeted and 22 Gy for non-targeted, respectively). Targeted nanoparticles had a greater retention in the tumor, but with a more heterogeneous dose distribution due to specific binding. No significant difference was found in normal tissue accumulation between the two agents, which then begs the question – is there a benefit to the targeted agent for this scenario? Non-targeted agents are much easier to implement in the clinic, and, as seen in Figure 4 in this article, the increased diffusivity of the non-targeted ^{177}Lu-AuNPs may allow for smoothing of the dose distribution, theoretically improving long-term impacts. Indeed, the authors concluded that “non-targeted

gold nanoseeds …would broaden the approach to tumors expressing many different phenotypes".

I.t. injection of radiotherapeutic agents, in theory, has promise in many cancer sites. Anywhere that traditional BRT is performed can also be accessed for i.t. injected BRT agents as well. However, the relative simplicity of i.t. injection in a xenograft model is not mirrored in the clinical setting – image guidance will likely be required for proper injections to be performed, as clinical tumors are normally not as superficial. Cine MRI, ultrasound, or fluoroscopic techniques may need to be employed. Regarding the evaluation of therapeutic response, precision caliper measurement was employed in this study. However, this is not a feasible technique in clinical trials – other methods should also be employed. Injection of PET agents such as ^{18}F-FDG, monitoring tumor metabolism, may provide a more reliable picture of the disease status (^{15}). CT and MRI may also find use in more accurate evaluation of tumor response, although their applications in breast cancer have been limited to date.

Considering the requirements of image guidance, as well as the dose heterogeneity of these ^{177}Lu-AuNPs as BRT agents, is there a benefit of i.t. nanoparticle delivery systems over traditional BRT or radionuclide therapy techniques? The answer seems to have two opposing sides: the limited diffusivity of AuNPs limits the normal tissue toxicities, but also degrades the tumor dose distribution. A nanoparticle system with enhanced diffusivity would improve homogeneity of the radiation doses in the target site, but may end up behaving more like an intravenously injected agent. Thus, much optimization is still required to find the right balance and ideal formulation. Future considerations such as the size of the AuNPs, different surface modifications, and the use of other radioisotopes may be worthwhile in pursuit of therapeutic optimization for LABC.

Overall, this intriguing study presents a topic that, if successfully clinically translated, may have immense impact in cancer outcomes. However, like all preclinical research, many aspects need to be optimized prior to clinical investigation, such as reducing the heterogeneity of dose distribution and employment of image-guided injections. Importantly, since the non-targeted agent was found to be as effective as the targeted agent, these ^{177}Lu-AuNPs may not only hold promise in the treatment of LABC, but also in many other cancer types/subtypes as well. We look forward to future preclinical and clinical studies with radiolabeled AuNPs in the years to come.

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