A New Type of Prostate Cancer Imaging: Will $^{64}CuCl_2$ PET/CT Flourish or Vanish?

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See the associated article on page 444.

In this issue of *The Journal of Nuclear Medicine,* Piccardo et al. (*1*) propose the use of $^{64}CuCl_2$ as an alternative PET radiopharmaceutical for investigating recurrent prostate cancer. The authors evaluated 50 prostate cancer patients with biochemical recurrence after definitive therapy (47/50 patients) or after palliative hormonal therapy (3/50 patients). Their specific aims were analysis of biodistribution and dosimetry and comparison of the diagnostic performance of $^{64}CuCl_2$ with that of ^{18}F-choline PET and multiparametric MRI (mpMRI). Copper concentration is generally increased in several tumors. Human copper transporter 1 is well represented in human cancers, including prostate cancer cells (*2*). However, the use of $^{64}CuCl_2$ as a PET tracer has not yet been extensively validated. Previously, the European Medicines Agency approved the use of $^{64}CuCl_2$ as a precursor for the radiolabeling of carrier molecules specifically developed and authorized for ^{64}Cu labeling (*3*). ^{64}Cu has been labeled with diacetyl-bis(N^4-methylthiosemicarbazone) and proposed as a PET radiopharmaceutical for hypoxia imaging (*4*), for instance. In addition, ^{64}Cu was labeled with prostate-specific membrane antigen (PSMA)–617 and recently used for investigating prostate cancer patients before surgery (*5*).

Piccardo et al. (*1*) report a $^{64}CuCl_2$ effective dose similar to those of ^{18}F-choline and ^{68}Ga-PSMA-11. $^{64}CuCl_2$ has a favorable biodistribution for imaging of prostate cancer, with no excretion via the urinary tract. This characteristic represents a potential advantage over ^{18}F-choline for evaluating the pelvis and prostatic bed. As expected, no drug-related pharmacologic effects or physiologic responses were observed immediately after the injection or up to 10 d afterward. From a diagnostic point of view in patients with biochemical recurrence, $^{64}CuCl_2$ PET/CT showed a higher detection rate than did ^{18}F-choline PET/CT and mpMRI. The detection rate for the assessment of lymph node metastases ($^{64}CuCl_2$, 32%; ^{18}F-choline, 30%; mpMRI, 28%) and bone metastases ($^{64}CuCl_2$, 8%; ^{18}F-choline, 8%; mpMRI, 10%) were approximately equal for both radiotracers. The main advantage for ^{64}CuCl2 was in the evaluation of local recurrence ($^{64}CuCl_2$, 64%; ^{18}F-choline, 30%; mpMRI, 50%).

Nevertheless, on a closer look, among patients with suspected local relapse, mpMRI and $^{64}CuCl_2$ PET/CT were concordant in 19 patients; 4 patients were $^{64}CuCl_2$ PET/CT–positive and mpMRI-negative; and 2 patients were mpMRI-positive and $^{64}CuCl_2$ PET/CT–negative. Although histopathologic confirmation is given for one patient in whom both $^{64}CuCl_2$ PET/CT and mp-MRI concordantly detected local relapse (Fig. 3), it remains unclear whether discordant cases were true- or false-positive by $^{64}CuCl_2$ PET/CT. As the authors noted, lack of histopathologic confirmation poses a significant limitation of this study, questioning the true superiority of $^{64}CuCl_2$ PET/CT over mpMRI. mpMRI is a well-established and widely validated technique for the detection of local recurrence of prostate cancer (*6*). Of note, ^{11}C-choline is cleared primarily via the hepatobiliary route and might have revealed higher local detection rates (*7,8*).

Several properties of $^{64}CuCl_2$ may limit its clinical use in prostate cancer patients: the decay of $^{64}CuCl_2$ is suboptimal for clinical PET/CT workflows. ^{64}Cu provides 18% β^+ decay at a half-life of 12.7 h. Accordingly, acquisition times need to be increased significantly to achieve the counting rates and image quality observed with ^{68}Ga-, ^{18}F-, or ^{11}C-labeled agents. Piccardo et al. performed PET/CT at 6 min per bed position, resulting in a 2–3 times longer total scan time than for ^{68}Ga-, ^{18}F-, or ^{11}C-labeled agents (2–3 min per bed position).

The authors also discuss the possible therapeutic effectiveness of ^{64}Cu delivered by emission of β^--radiation and Auger electrons. Previously, Auger therapy has been applied in patients with neuroendocrine tumors by targeting the somatostatin receptor (*9*). However, because of low response rates, more effective β^--emitting probes were developed and approved (*10*). Dosimetry reveals the highest $^{64}CuCl_2$ uptake in the liver, with an approximately 10 times higher radiation dose than that with ^{68}Ga-PSMA. The liver is generally considered a radiosensitive organ, with increased rates of severe hepatitis and liver failure beyond an 18-Gy total organ dose. Thus, the low efficacy of Auger therapy, and the high liver radiation dose, might limit the therapeutic potential of $^{64}CuCl_2$.

In conclusion, $^{64}CuCl_2$ imaging is feasible, with a favorable biodistribution and dosimetry. We congratulate Piccardo et al. for reporting high $^{64}CuCl_2$ PET/CT detection rates in patients with biochemically recurrent prostate cancer. The results of their study

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will support a discussion of the use of $^{64}CuCl_2$ or ^{64}Cu-labeled probes for imaging prostate cancer and other malignancies. Initial data for prostate cancer detection are promising, but further work is needed. The included comparator, that is, choline PET/CT, has been considered suboptimal by most academic PET facilities, which have transitioned to PSMA-directed PET/CT or ^{18}F-fluciclovine PET/CT over the past 2 y (*11*). We encourage a head-to-head comparison using central image interpretation to investigate the current additional value of $^{64}CuCl_2$ as compared with currently available receptor-based radiotracers such as ^{68}Ga-PSMA-11 or metabolic radiotracers such as ^{18}F-fluciclovine.

Whether $^{64}CuCl_2$ will become a real option for prostate cancer diagnosis will clearly depend on its performance compared with PSMA ligands and its regulatory approval and reimbursement.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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