The Hierarchy of SUVs: From Diagnostics to Therapeutics and the Pathway to Effective Theranostics

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Over 80 y ago, Saul Hertz pioneered medical use of ^{131}I, successfully treating patients with benign and malignant thyroid conditions. Today, it still remains our exemplary theranostic. ^{124}I PET/CT, used for imaging of thyroid cancer, boasts the highest tumor-to-background contrast among oncologic radiopharmaceuticals, directly translating to our ability to cure patients with advanced metastatic disease using a theranostic approach. In recent years, radiolabeled peptides targeting the somatostatin receptor and the prostate-specific membrane antigen (PSMA) receptor have become new standards of care for treating neuroendocrine and prostate cancers, improving the lives of many patients. Although the treatments are highly effective and improve both survival and quality of life, they mainly offer palliative outcomes, unlike ^{131}I, which often achieves complete lifelong responses.

At its core, a theranostic is essentially a radiation delivery device. The mechanistic cause-and-effect targeted tumor-killing ability is unique in modern medicine. The simplicity of radioiodine's leveraging of the sodium iodine symporter to pump radiation to thyroid cancer cells remains unparalleled. When Saul Hertz first administered ^{131}I, he was able to confirm specific uptake with external counting but was unable to image it. Now with ^{124}I and PET/CT, we can visualize and quantify total-body biodistribution. The target-to-background contrast is astounding, with SUV_{max} surpassing 1,000 and frequently reaching the 100 s. Moreover, delayed imaging at 24 to 48 h demonstrates tumor retention and washout from normal organs. This is a surrogate of more formal dosimetry calculations, confirming high tumor targeting with doses exceeding 100 Gy and a dose–response relationship (*1*). Patients with disease progression or stable disease responses received tumor doses of less than 75 Gy.

Advances in radiochemistry paved the way to transition from unlabeled radioiodine to somatostatin receptor/PSMA theranostics using radiolabeled peptides to target cell-surface receptors. These treatments are highly effective and exceptionally well tolerated.

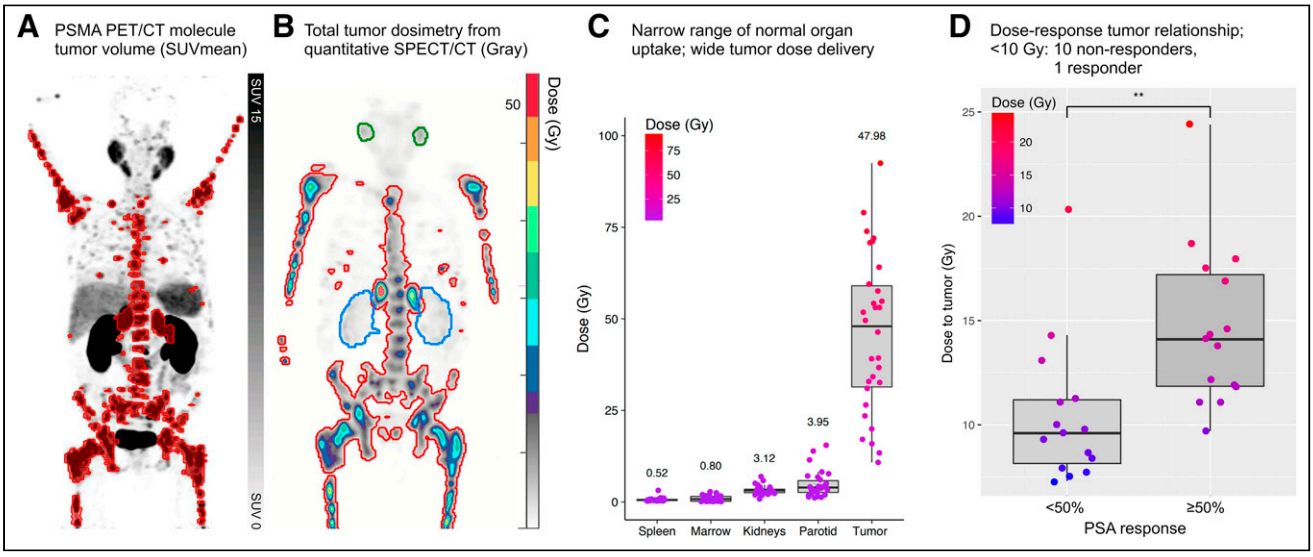

FIGURE 1. Theranostics is not magical: radiation delivery to tumor is required for response. (A) Pretreatment PSMA PET/CT (SUV > 3 in red). (B) Post-therapy voxel-based dosimetry based on multiple-time-point SPECT/CT. (C) Narrow range of dose to normal tissues but wide range to tumor. (D) Dose–response relationship demonstrating that high tumor targeting is required for response. Adapted from (*4*).

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Complete and durable responses can be seen but do not occur for most patients. Development of resistance or recurrence is invariable. Somatostatin receptor or PSMA PET/CT enables selection of patients using different criteria. For PSMA PET/CT, the 2 randomized trials used different criteria: intensity greater than liver in VISION (*2*), equating to an SUV of 5–7, compared with an SUV_{max} of over 20 in TheraP (*3*). SUV_{max} can reach several hundred but is typically much lower. Like radioiodine, a dose–response relationship has been demonstrated (Fig. 1) (*4*). Strong evidence from these randomized trials confirms that pretherapeutic PSMA PET/CT can be used as a predictive biomarker (*5,6*).

These recent discoveries were led by academic nuclear medicine departments (*7–9*) in which novel compounds were transitioned from laboratory to small-animal models and then rapidly to humans. Images with striking tumor-to-background contrast provided pioneering physicians with the confidence to test novel strategies on a compassionate-access basis in patients for whom standard therapeutic options had failed. These "$n = 1$" cases led to case series and eventually to randomized trials, a prerequisite to enable regulatory approvals and widespread availability.

The last few years have seen an explosion of investment and commercial development of new radiopharmaceuticals. This is welcome and long overdue given the immense value theranostics can afford to improve patient outcomes. With this investment, we are seeing a switch to a more traditional drug development pathway for new radiopharmaceuticals from an early stage. Some protocols are combining first-in-humans phase 0 biodistribution PET/CT studies and a phase 1 dose-escalation design for radionuclide therapy.

Putting safety and normal biodistribution aside, the success of treatment is wholly dependent on favorable tumor targeting. Futility can be predicted from PET/CT imaging and posttherapy SPECT/CT dosimetry. Experience from successful theranostics to date suggests that high SUVs on PET/CT are a prerequisite for successful radionuclide therapy with β-emitters such ^{177}Lu or ^{131}I. Protocols requiring tumor uptake above background—enabling patients to have an SUV of less than 1—are not in the best interest of any patients. This degree of tumor targeting has no chance of improving outcomes and, accordingly, should not be approved by ethics committees (Fig. 2). Additionally, delayed posttherapy SPECT/CT is critical because tumor retention is also a prerequisite for efficacy. For example, anecdotal experience with PSMA targeting for tumor types other than prostate cancer, for which expression is in the tumor microvasculature rather than the cell surface, suggest that washout occurs by 24 h. Both high uptake and tumor retention are required to improve patient outcomes.

There remain areas of uncertainty. The higher linear energy transfer of α-emitter therapy provides immense promise for next-generation theranostics. Although prospective evidence is limited for any α-labeled radioligand therapy, we do have strong evidence for the effectiveness of ^{223}Ra. Uptake can be quantified using pretherapeutic NaF PET/CT; an SUV_{max} of as high as 100 can be observed, as well as correlations with the prostate-specific antigen response (*10*). Whether lower uptake in tumors with α-therapies than with β-therapies can be successful remains unanswered. This is of particular interest in exploring therapies when normal-organ activity is very low, possibly with radionuclides targeting fibroblast-activating protein. Auger emitters are another unexplored domain. If they can reach the nucleus adjacent to DNA, it is possible that pretherapeutic imaging may have a more limited role in patient selection. Furthermore, imaging-based dosimetry may be unable to measure effects of Auger electrons.

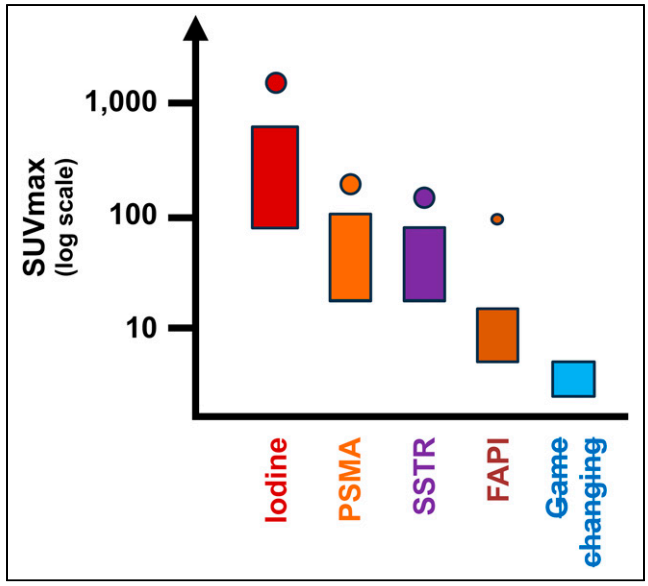

FIGURE 2. Hierarchy of SUVs: from left to right, ^{131}I, PSMA, somatostatin receptor (DOTATATE), fibroblast activation protein inhibitor, and purported next-generation theranostic. ^{131}I has uptake that is unmatched by any other radiopharmaceutical.

As we peer into the future of nuclear medicine, the promise of transformative theranostics looms large. Surely, we can beat decades-old radioiodine and find new targeted agents with even more impressive tumor uptake. This possibility offers hope for truly game-changing theranostics with curative potential. Yet, as we navigate these promising avenues, it is crucial to remain grounded in evidence rather than fall prey to magical thinking. We know that high tumor doses are a prerequisite for meaningful antitumor activity. Pretherapy PET/CT imaging and posttherapy dosimetry provide a critical yardstick. These tools allow us to promptly abandon agents that have no or a very low likelihood of benefiting our patients. To catapult nuclear medicine forward in this new era of precision oncology, we need to adapt. Hybrid approaches learned from $n = 1$ approaches and oncologic phase 1 approaches are needed to propel our field forward.

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