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Economics of New Molecular Targeted Personalized Radiopharmaceuticals

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Nuclear medicine has come a long way since 2007 when Adrian Nunn pointed out the approval of radiopharmaceuticals was at an all-time low with all the major radiopharmaceutical agents in use having been approved over 10 years ago. Challenges being the prohibitively high cost of drug development and the large number of drugs failing in clinical trials. Proceed to today where molecular imaging is fast-tracking the drug discovery process by reducing both the time and cost to screen candidates by quantitating the drugs effect on the target and toxicity to normal tissues. Nuclear medicine is now leading medical practice in personalized medicine using the theragnostic approach. Theragnostics is defined as the use of molecular diagnostic techniques in real time to stratify patients to guide treatment decisions such as the choice of drug, the dose of administration, and the timing of drug delivery for a given patient. Enabling visualization and quantitation of in vivo function of the whole body and thus patient heterogeneity and variability informs the physician on how to treat an individual patient. Recent successes such as the Food and Drug Administration approval of Lutathera and NETSPOT have resulted in an increasing number of pharmaceutical companies pursing theragnostics further heightened by the purchase of Advanced Accelerator Applications for 3.9 billion by Novartis and Endocyte, Inc for 2.1 billion. Theragnostics are further aiding drug development by showing which agents are most viable and reducing the overall cost of bringing a drug to clinical trials and regulatory approval. This is indeed a renaissance for nuclear medicine in which the acceptance of imaging to inform and monitor therapy has been embraced and even required by the Food and Drug Administration for the clinical evaluation of targeted therapeutic radiopharmaceuticals showing there is indeed a viable business model for targeted theragnostic radiopharmaceuticals and personalized medicine.
Semin Nucl Med 49:450-457 © 2019 Published by Elsevier Inc.

Traditionally medicine has relied on the concept that a single drug could be developed that would treat all patients. Further that dosage could be determined and delivered based solely on the patient's weight. This paradigm has worked but due to the complexity of disseminated disease a new paradigm is needed to tailor individual treatment to attain the highest efficacy and reduce toxicity in individual patients. A major challenge is the diversity and heterogeneity observed in patient populations. For example, traditionally we have diagnosed patients based largely on imaging gross anatomy and observing structural abnormalities referred to as anatomical imaging. However, what we know is that patient cancers function differently and that each patient's disease is unique. Previously patients who were diagnosed with metastatic cancer underwent surgery to have tissue samples removed and analyzed externally to determine the tumor pathology and guide the choice of drug. Tissue samples, however, do not give you a total picture of the patient's tumor or aid in determining how many tumor sites the patient has, how much uptake of the drug each of these sites will have, and/or how much of the drug will be taken up in normal tissues resulting in toxicity. Development of new imaging techniques with higher resolution, advent of radiotracers or biomarkers and animal models of human disease has facilitated functional imaging.[1] This type of imaging is critical where we are evaluating patients with disseminated disease that is not easily treated with surgery or external beam therapy. In these cases, patients need more complicated treatments and are finding cures limited due to the

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 https://doi.org/10.1053/j.semnuclmed.2019.07.002
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drug not binding to the target or in significant quantities to be effective, to the toxic side effects that arise from the drugs themselves on normal tissue. Due to the advent of theragnostics, patients are now able to get a patient-specific diagnosis that directs the physician in determining the best drug for the patient, the best dose, and the best dose delivery that will result in optimal treatments called precision medicine. This has led to the concept of theragnostics in which a drug is developed that can be used to initially image the patient and more specifically quantitate the uptake of the drug in the tumor sites and in the normal tissues. Further it allows for determining the clearance of the drug and thus the effectiveness of the treatment on the tumor and the toxicity on normal tissues. The overall arching aim being to deliver agents at levels capable of ablating disease leading to cures.

As medicine has moved more toward targeted therapy applications in which targeting vectors are used to deliver cytotoxic payloads to diseased sites it has become more necessary to ensure these drugs are being delivered in sufficient quantity to the desired destination. Radionuclides due to their short half-lives which result in them delivering cytotoxicity in high doses for a short time and then decaying to stable elements that pose no threat have grown in interest. Particularly those that offer the opportunity to be visualized by ex vivo imaging to assess how each patient handles the drug and thus to enable the physician to determine what drug to give the patient, in what dose and at what time and thus improved patient management. Further the patient can be imaged after the drug has been given to monitor therapy.

This is not a new concept for nuclear medicine as radioiodine imaging and treatment of thyroid tumors can be traced back to the pioneering work of Glenn Seaborg and John Livingood who in 1938 at the University of California, Berkeley discovered radioactive iodine-131. This radioisotope became the gold standard in the diagnosis and treatment of thyroid cancer which is used in nuclear medicine imaging departments throughout the world. An initial low dose of Iodine-131 was given to evaluate the uptake in the thyroid tissue and clearance to ensure toxicity was low enough to use I-131 for ablation. This method has worked very well, and, in most cases, imaging is not needed, although some publications have determined that a small population of patients may not be receiving enough dose while others are receiving too high of a dose and that imaging would mitigate these situations.

Preimaging was initially performed with low doses of I-131. Concern with the use of I-131 was that it could result in "stunning" leaving the tissue less avid for I-131 and thus resistant to further treatment. This led to looking for indirect methods of imaging in which "sister" imaging radionuclides which had better imaging properties could initially be used to inform therapy. There are two other iodine radionuclides I-123 that has a short half-life of 13 hours and a 159 KeV photon (83%) which is ideal for single photon emission computed tomography (SPECT) imaging and I-124 that decays giving off a positron (52%) that annihilates with an electron resulting in bilateral 511 KeV photons and can be used for positron emission tomography (PET) imaging. The use of I-123 for diagnostic scans may be a lower dose route to achieve high-quality pretreatment images and clinical evaluation has demonstrated they were highly comparable to I-131 dose distribution, resulted in better imaging quality and reduced dose to the patient.[2] Shown in Figure 1 is a patient with a pretreatment scan using I-123 and a post-treatment scan using I-131. Study demonstrated that diagnostic scanning with I-123 was highly comparable to high-dose I-131 post-treatment scans. More metastatic sites may be identified post-treatment with I-131 due to the much larger amounts of radioactivity administered.

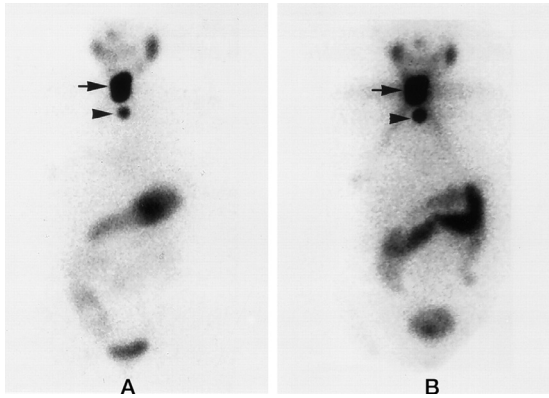

Figure 1 Thyroid bed (arrows) and a lymph node metastasis (arrowheads) noted on the anterior view of a 370-MBq ^{123}I pretreatment scan (A) and a 7252-MBq ^{131}I post-treatment scan.[2]

Imaging offers advantages over traditional methods used in drug discovery such as blood and tissue samples (dissection) and histology which are costly and time consuming and reduces the number of animals needed. Imaging reduces the overall workload required for biodistribution studies necessary for target candidate comparisons and speeds up the evaluation and down selection of lead drug candidates.[2] Imaging allows for patient stratification and the ability to conduct longitudinal studies in a single animal.[2] Further molecular imaging can provide a much earlier indication of therapy success or failure. This enables a company to determine lead candidates earlier in the process and thus not waste money and time on nonviable candidates. Imaging also saves costs by stratifying patients from receiving costly therapies that either are shown not to be working or that imaging shows will not be effective in a given patient.

Imaging is extremely informative as we move to utilizing radiopharmaceutical-targeted therapies that are becoming even more relevant particularly in patients with disseminated disease that have demonstrated resistance to standard of care treatments. Targeted therapies are now being evaluated and implemented that use a variety of targeting agents from small molecules to peptides, antibodies and there is growing interest in utilizing nanoparticles. Criteria for the targeting agent are its level of expression be related to the disease, must be accessible, high expression on the diseased cells with minimal expression on normal cells. Additionally, the expression should be stable during the progression of the disease. It would be preferable if the target expression was homogenous. The advantage of these targeted approaches is there specificity to target and interfere with pathways specific or

overexpressed in cancer cells and thus mitigates toxicity to normal cells.[3] Challenges with targeted therapies are not all patients will respond, dose needs to be tailored to the patient, responses may be short lived and as recently demonstrated successful treatments may require choosing the optimal radionuclide to ensure optimal dose and minimal toxicity.[4] This is why imaging with these targeted approaches is so important as it allows the physician to stratify patients and determine the dosing and timing of delivery to ensure optimal outcomes. Further advantage of imaging is it can be used to monitor response informing the physician in real time if the patient is responding favorably to the treatment. Radiopharmaceutical-targeted treatments tend to be more cost effective than standard chemotherapy treatments which require multiple doses over a longer period of time, however, they are not cheap and the earlier a physician can determine that a patient is not responding the more costs can be saved by not treating a patient with drugs that are not effective for that patient and even toxic. Thus, theragnostics are critical for successful application of targeted therapies and although the imaging may lead to some small additional costs upfront it saves costs in ensuring patients are not receiving ineffective treatments.

Theragnostics require the use of a diagnostic, a radionuclide, that gives off photons that can either be imaged externally using SPECT or PET which has advantages in resolution and quantitation. Theragnostics facilitates medical decision making and thus enhances the management of patients. To do this, it is necessary to choose the best radionuclide and attach it to the targeting vector to enable ex vivo imaging. There are typically two different approaches that theragnostics have been implemented; one is to use the same radionuclide for both the imaging and therapy such as demonstrated in the earlier example of using I-131 for both the imaging and therapeutic radionuclide as its decays result in both the production of photons which can be imaged and beta particles for ablation of cells. This has loosely been termed the direct method and is ideal as the imaging is directly reflective of the therapeutic agent. Only a handful of radionuclides have both an imaging component and a therapeutic component and thus the use of theragnostic pairs of radionuclides has been implemented often referred to as the indirect approach. In the indirect approach, theragnostic isotope pairs are used that contain a radionuclide with ideal properties for imaging that is attached to the targeting vector and administered for diagnosis and then an isotope of the same element with the same chemistry but nuclear properties more suited for therapy typically particle emitters are attached and used for therapy. An example of which is the radionuclide pair Copper-64 (Cu-64) and Copper-67 (Cu-67). The Cu-64 decays with a half-life of 12.8 hours giving off a positron (19%) which can be easily detected and quantified by PET, the Cu-67 decays producing a desirable beta particle (0.57 MeV) with a half-life of 2.58 days. As the chemistry is the same, no differences are observed in the pharmacokinetics of the diagnostic or therapeutic agent. The second mode termed indirect imaging is to utilize theragnostic radionuclide pairs that differ in their chemistry but can supply the needed imaging data to inform therapy. Examples are the use of Gallium-68 (Ga-68) which is a short-lived positron emitter (half-life of 68 minutes) which is used to inform the therapy of a variety of targeted therapeutics using such radiometals as Yttium-90 (Y-90), Lutetium-177 (Lu-177), and Actinium-225 (Ac-225). In this case, it is important to pick a diagnostic with a long enough half-life that it matches the biological half-life of the targeting vector to allow the physician to determine if uptake is enough to ensure success of the treatment. Thus, in the case of antibodies that can require multiple days to achieve maximum uptake in the tumor and the short-lived Ga-68 is not an appropriate choice but longer lived radionuclides such as Zirconium-68 (Zr-68) and Indium-111 (In-111) and Arsenic-72 (As-72) are better choices. The major challenge with using radionuclides of different elements is that differences in the chemistry and thus structure of the diagnostic radiolabeled vector compared to the therapeutic radiolabeled vector can result in variances in target uptake as well as disparities in normal tissue uptake and clearance. These variations can result in an over or under estimation of the actual dose that is being delivered. This review will not cover all the radionuclides that can be used or methods of attachment as that has been thoroughly covered in the previous articles in this special review but provide examples how theragnostics have enhanced patient management and outcomes.

For targeted therapy applications, it can be essential to use imaging as it enables early detection, staging, therapy selection, planning, and monitoring of treatment response. This enables the physician to screen patients and determine which patients should proceed with treatment and which should be excluded due to less than optimal target expression. This has traditionally been done by taking biopsy samples from the patient's tumor and lymph nodes and performing analysis such as immunohistochemistry (IHC). These are in vitro assays using antibodies to determine if the biopsied tissues are positive or negative for target expression. Advantages of this method are it is simple to use, cheap, and can be performed in most pathology labs.[5] IHC suffers from not giving a complete picture of the whole tumor and its target expression as well as not indicating what the expression or uptake is in normal tissue. Often heterogeneity in target expression is observed in tumors and in different lesions which further can change with time and treatment. To get a complete picture, multiple tissue biopsies would be required which is not feasible in patients with extensive metastatic disease.[5] Immunoassay such as enzyme-linked immunosorbent assay (ELISA) or flow cytometry can also be used to determine the amount of antigen in serum, plasma, or other body fluids.[6] Flow cytometry measures antigen expression in single cells from a suspension and can be used to determine antigen expression on blood cell subtypes.[7] Both ELISA and flow cytometry are relatively easy to use and readily available, however, they suffer from subjective interpretation of the results and due to arbitrary threshold settings, there is no straight forward difference between positive and negative samples.[5] Further as with IHC techniques they suffer from giving limited information on only a small number of tumor

cells and thus whole body antigen expression and drug pharmacokinetics is not evaluated. The hospitalizations and risk-associated biopsies combined with the risk of false positives and patient distress further highlight the disadvantages of these methods.

Whole body target expression and drug pharmacokinetics informing patient selection and treatment can most effectively be done by using the molecular imaging techniques of SPECT and PET. Information about the biodistribution of the therapeutic compound can be determined informing dose and timing of delivery prior to administration of high levels of radioactivity to the patient. Both SPECT and PET molecular imaging techniques require the targeting vector be labeled with a radionuclide that decays generating photons with high enough emission that they exit the body and can be detected and collimated giving a full 2-D or 3-D representation of target expression and drug pharmacokinetics including drug metabolism and clearance. The information derived from these techniques is clearly more informative than those from any of the traditional used in vitro methods such as IHC, ELISA, and Flow cytometry, is noninvasive and gentler to the patient. Further they can be performed at multiple intervals to assess changes in antigen expression as treatment proceeds informing both efficacy and treatment management. Such techniques inform patient selection, dosimetry and response to therapy.

Examples of targeted therapy cases of personalized medicine using theragnostics to inform patient management are those for the treatment of non-Hodgkin's lymphoma using two Food and Drug Administration (FDA)-approved radioimmunotherapies—Bexxar and Zevalin. The addition of the therapeutic radionuclide enables tumor cell ablation and the cross-fire effect from the beta particles can result in the death of cells not specifically targeted which is not possible with the immunotherapy alone. Zevalin was the first radioimmunotherapy drug approved by the FDA in 2002 and consists of the murine monoclonal antibody ibritumomab that targets the CD20 antigen conjugated to tiuxetan a modified diethylenetriamine pentaacetic acid (DTPA) chelator radiolabeled with Y-90 for therapy.[8] As Y-90 lacks an imageable photon emission (Bremsstrahlung imaging is possible but results in poor imaging) the In-111 diagnostic analog was used for imaging to confirm the organ specific biodistribution of the Y-90 therapeutic and to determine dosimetry prior to treatment with the Y-90-labeled ibritumomab tiuxetan. Zevalin was approved for the treatment of patients with relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma, including patients with rituximab refractory follicular non-Hodgkin's lymphoma.[8] The Zevalin regime involved administering 250 mg/m^2 of the Rituximab followed by 5 mCi (1.6 mg) of In-111-labeled ibritumomab tiuxetan for diagnostic scans. After images at 24, 48-72, and 120 hours showed tumor localization and minimal normal tissue uptake in the bone marrow and spleen which occurred in ~0.6% of cases shown in Figures 2 and 3. A 0.3-0.4 mCi/mg dose of Y-90-labeled ibritumomab tiuxetan (maximum dose of 32 mCi) was administered. A major limitation to the use of Zevalin was its high cost of $37,000.00 in US dollars.

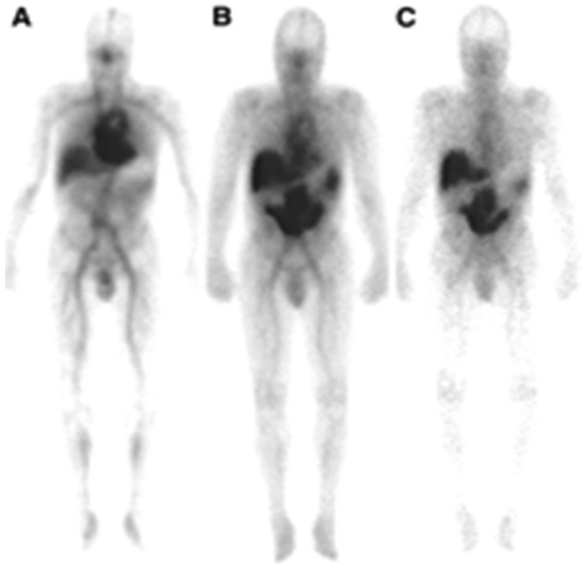

Figure 2 Whole-body gamma-camera scans at 24, 72, and 120 hours after administration of ^{111}In-ibritumomab tiuxetan. Radiolabeled antibody is evident in blood pool at 24 hours (A), with tumor localization seen in abdominal mass, liver, and spleen at later time points (B and C). Picture reprinted courtesy of J Nucl Med. 44, 3465-3474, 2003, Wiseman et al.

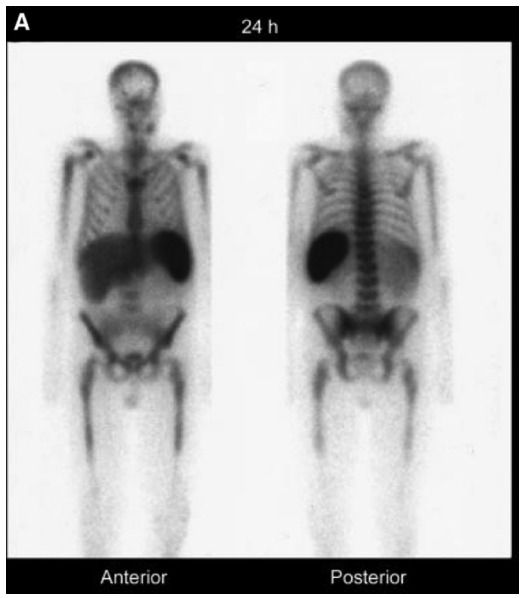

Figure 3 Altered biodistribution of ^{111}In-ibritumomab Tiuxetan showing enhanced uptake in the bone marrow and spleen. Image taken 24 hours post injection. Image Permission of J Nucl Med. 2005, 46, 1812-1818, Conti et al.

The radiopharmaceutical Bexxar which required an initial diagnostic image to inform patient dose and selection was approved for the treatment of relapsed or chemotherapy/Rituxan – refractory non-Hodgkin's lymphoma in 2003.[9,10] It was comprised of the antibody Tositumomab a murine IgG2a lambda monoclonal antibody directed against the CD20 antigen and was administered as the unlabeled Tositumomab and the Tositumomab radiolabeled with I-131.

Administration with the unlabeled monoclonal antibody was to prevent excessive uptake in the spleen and bone marrow.

Due to some of the challenges observed with antibodies including immunogenicity, slow accumulation, normal tissue toxicity, poor tumor penetration, difficulty in synthesizing, and modification of antibodies a new area of theragnostics was developed in using modified peptides for imaging called peptide receptor scintigraphy and peptide receptor radionuclide therapy. The first such use occurred in the 1980s with the development of I-123-labeled Tyr^3-octreotide a peptide analog of somatostatin for the localization of carcinoid tumors, paragangliomas, and pancreatic tumors which highly express somatostatin receptors which somatostatin has a high affinity for.[11] This was closely followed by the development of In-111-penetreotide which was comprised of the octreotide peptide attached to a DTPA chelator for stable complexation of In-111 referred to as Octreoscan. The In-111-labeled Octreoscan exhibited better sensitivity and specificity and became the first FDA-approved peptide-based radiopharmaceutical in 1994.[12,13] Octreoscan treatment resulted in modest tumor shrinkage followed with an associated risk of developing leukemia.[14] Researchers began to look at other radiometals and changed out the DTPA chelator for DOTA which is able to stably complex a variety of radiometals.[15] This modification resulted in an increase in the amount of activity retained in the kidneys which was mitigated by the introduction of amino acid infusions to protect the kidneys. Novartis launched Y-90-labeled DOTA-Tyr^3-octreotide (DOTATOC) in 1997 which proved to be more effective but was accompanied with higher renal toxicity.[16,17] Shortly after this Ga-68-labeled DOTATOC was introduced for PET imaging.[18] Owing to the renal toxicity observed with Y-90 the search was on for radiometals that could result in lower toxicity and investigations of Lu-177-labeled DOTATOC with its shorter range beta particle and similar chemistry to Y-90 were begun and that with combined amino acid infusions proved to be an effective therapeutic and resulted in an overall increase in survival of patients. A modified octreotide peptide version DOTATATE was brought to the clinic by Advanced Accelerator Applications (AAA) along with the Ga-68-radialabled DOTATE later termed NETSPOT into clinical trials and it received orphan drug status in March 2014 by the FDA and the European Medicine Agency. NETSPOT was approved by the FDA in 2016 for PET imaging to locate somatostatin receptor positive neuroendocrine tumors in adult and pediatric patients. The Lu-177 labeled DOTATATE (Lutathera) the therapeutic analog of NETSPOT shown in Figure 4 was taken into clinical trials by AAA and approved by the FDA in 2017 shown in Figure 5. The use of the diagnostic NETSPOT resulted in a change in patient management decisions in 71% of cases.[19] Facilitating the ability to select

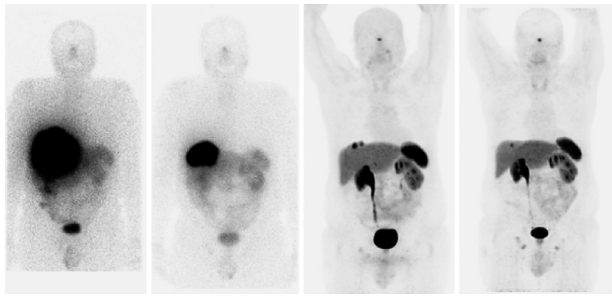

Figure 5 Response to ^{177}Lu DOTATATE – PRRT in a rectal NET with a massive (21.5-cm diameter) inoperable right lobe liver metastasis. Treatment with ^{177}Lu DOTATATE every 8 weeks. ^{68}Ga DOTATATE images are immediate postinitial treatment, and every 8 weeks. Last image, on right, liver lesion has shrunk to 1.5 cm. (43 GBq cumulative activity). Reprinted courtesy of JNM.

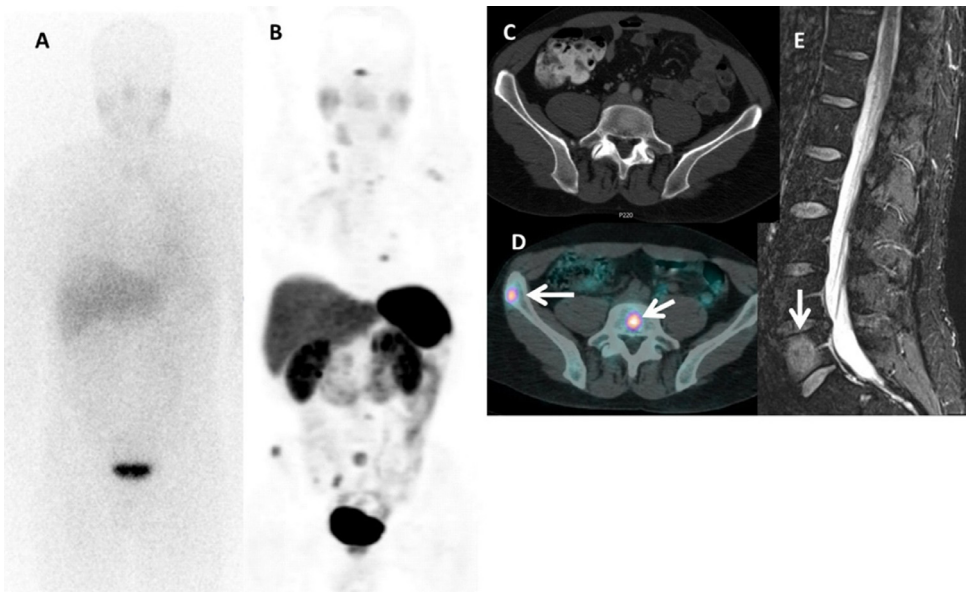

Figure 4 (A) ^{111}In Octreotide SPECT/CT false-negative, (B) ^{68}Ga DOTATATE true positive, (C) contrast CT, (D) PET/CT reprinted courtesy of JNM. Deppen SA et al. Safety and efficacy of ^{68}Ga DOTATATE for diagnosis, staging, and treatment of neuroendocrine tumors. J Nucl Med. 2016.115:163865.

patients for Lutathera therapy, design the treatment regime including dose determination, and monitor treatment informing treatment follow-up.[19] The NETTER-1 Phase II trial showed a progression free survival in the range of 30-40 months and a 79% reduction in the risk of disease progression or death. Lutathera has also been shown to improve several quality of life issues variables including diarrhea.[19]

Prostate-specific membrane antigen (PSMA) is upregulated in prostate cancer and is minimally expressed in nonprostate tissues. The antibody J591 can be used for immunotherapy of prostate cancer but doses equal to or greater than 100 mg are required and complexation with toxins or radionuclides which require lower amounts of J591 have been shown to be a better approach.[20] For use in radioimmunotherapy, J591 was covalently coupled with 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid (DOTA), a chelating agent that stably binds a variety of radiometals.[20] Clinical evaluations have been performed with both Y-90 and Lu-177 in metastatic-resistant prostate cancer patients with promising results.[21,22] Lutetim-177 labeled to J591 can be used for both imaging and therapy as it decays (half-life 6.64 days) resulting in a 113 Kev (6.6%) and 208 KeV (11%) photons and 0.498 MeV beta particle. Figure 6 shows a patient image after treatment receiving an injection of Lu-177-J591. Noninvasive molecular imaging of PSMA expression proved to be a predictive biomarker, since patients with poor PSMA imaging were less likely to respond to Lu-177-J591 therapy.[22] Indium-111-labeled PSMA was evaluated as a diagnostic for patient selection and dose determination of treatment with J591 labeled with either Lu-177 or Y-90. This was advantageous as in the case of Lu-177 it eliminated patient exposure to the beta particle emission. Biodistribution patterns were generally the same, however, differences were noted in the liver, lung, and spleen uptake which was slightly higher for In-111 in contrast to Lu-177 and Y-90.[20,22] This was unexpected but is attributable to the slight differences in complexation chemistry of the radiometals. The radiation dose to the liver may be overestimated by as much as 25% based on In-111 data used for Y-90.[15,17] Multiple administrations of Lu-177-J591 and Y-90-J591 were tolerated and imaging could be used to monitor treatment response.[20-24]

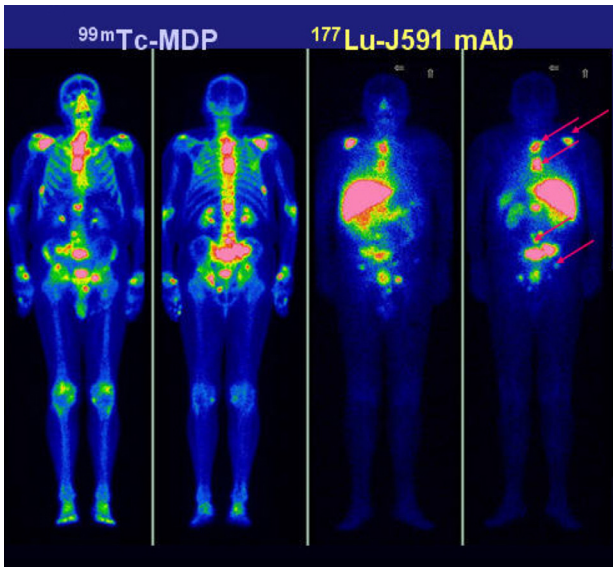

Figure 6 Shown on the left is a SPECT image of a patient with androgen-independent prostate cancer 2-3 hours after injection of 740 MBq of ^{99m}Tc-MDP showing the metastatic foci in the bone. Shown in the right is the same patient 7 days after injection with 2.59 GBq/m^2 of ^{177}Lu-J591 showing the uptake in the prostate and at the metastatic sites in the bone (shown by red arrow).

Several small urea-based ligands molecules have since been developed and are undergoing clinical evaluation for targeting the PSMA that when radiolabeled with radionuclides can be used as theragnostics for managing metastatic castration resistant prostate cancer. PSMA-11 labeled with Ga-68 is being used as an imaging surrogate for PSMA-617 which is conjugated to the DOTA chelator and can bind metals such as Lu-177 and Ac-225.[25-27] PSMA-617 was developed for therapy of castrate resistant prostate cancer and has optimal tumor penetration with lower kidney retention. These small urea-based ligands have advantages over the monoclonal antibody J591 in that they accumulate much quicker in the metastatic lesions and clear faster from normal tissues resulting in lower overall doses particularly to the liver and bone marrow. Further the smaller molecules allow for the selection of radionuclides with shorter half-lives for conducting the imaging such as Ga-68 and even F-18. The Lu-177 labeled PSMA-617 is currently undergoing clinical trials and has demonstrated good dosimetry and is well tolerated. Despite this about 30% of patients either show resistance to treatment and some patients show diffuse red bone marrow infiltration an indicator of hematologic cannot tolerate treatment with Lu-177-labeled PSMA-617.[28,29] This has led to the evaluation of alpha-targeted therapy in these patients. Shown in Figure 7 is a patient that upon imaging with Ga-68-labeled PSMA-11 was determined to be a good candidate for treatment with Lu-177-labeled PSMA-617 and was given two fractional treatments. Imaging after those two treatments as shown in the figure showed the tumors were not responding and even growing appearing to be resistant to the Lu-177-labeled PSMA-617 treatment. The patient was then switched to treatment with the Ac-225-labeled PSMA-617 receiving three cycles of 6.4 MBq (100 kBq per kilogram of body weight) at bimonthly intervals.[28] As the images show the patient's tumors began responding after two treatments and his PSA values dropped to levels after the third treatment that indicate a complete response. A second patient shown in Figure 8 entered into the same trial was imaged with Ga-68-PSMA-11 which showed high uptake in the red bone marrow indicating the patient was not a good candidate for Lu-177 PSMA-617 as the long range of the beta particle would be too toxic. The patient was instead given three cycles of 6.4 MBq (100 kBq per kilogram of body weight) at bimonthly intervals.[28] Similar results were observed for this patient in that the PSA vales dropped from over 3000 to less than 0.1 nM indicating a complete response.[28] Theragnostics played a critical role enabling the patient who was not responding to be quickly taken off an ineffective treatment and switched to one that resulted in a complete response.

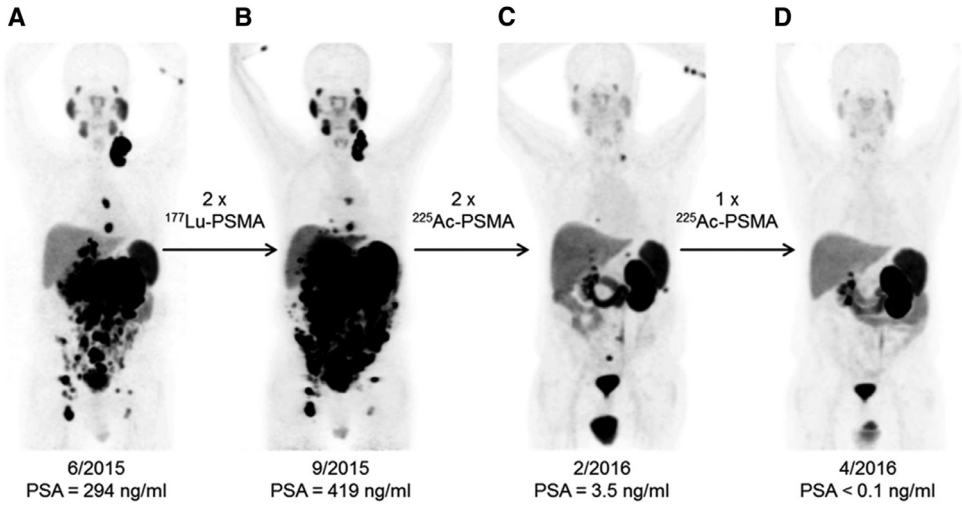

Figure 7 ^{68}Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting 177Lu-PSMA-617 presented progression (B). Reprinted from Kratochwil et al.[28]

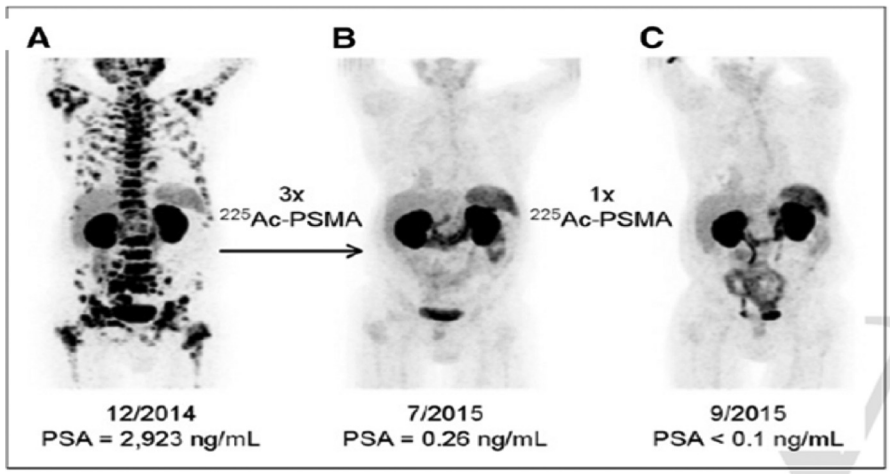

Figure 8 ^{68}Ga-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 months after third cycle of ^{225}Ac-PSMA-617 (B), and restaging 2 months after one additional consolidation therapy (C). Reprinted from Kratochwil et al.[28]

The second patient with imaging showed the planned treatment would have been too toxic and was switched to a treatment with a radionuclide with lower tissue penetration but that could deliver significant dose. Both cases the imaging facilitated patient management and enhanced patient outcome.

It can be seen from the listed examples that the use of theragnostics to deliver personalized treatments enhances patient outcome and quality of life and reduces costs by reducing unsuccessful treatments, lowering the costs of clinical trials due to the stratification of patients, and lowering drug development costs. Despite this there still remain challenges to getting these personalized treatments developed. The reimbursement for imaging agents has been inadequate for some time as they are perceived to be high cost with low value. Additionally, the costs for these theragnostic targeted drugs are high and the reimbursement budgets are limited. When Zevalin was first approved it was the most expensive drug on the market. If one considers that chemotherapies are actually given in multiple does over a longer period it is actually seen that the costs of these treatments are more cost effective. Additional barriers are the growing regulatory burden required to produce and administer these agents. This becomes even more expensive when it is recognized that different countries operate under different regulations including those regarding the manufacturing of the agents and the clinical trials. If these could be harmonized one could foresee a drug only needing a single clinical trial in one country that upon successful completion would result in a drug that would be accepted in multiple countries and thus make it more profitable than the current model of repeating trials in each country to obtain approval. There are ongoing efforts by societies such as the SNMMI, the IAEA, EANM, and the CANM to work toward harmonization but this will take some time. Despite these challenges, recent successes of combining the imaging agents with the therapeutic have demonstrated reductions in the failure rate and thus lowered risk of drug development in the later most expensive phases of drug development. This is most clearly

reflected in the acquiring by Novartis of AAA for 3.9 billion and Endocyte for 2.1 billion. The theragnostics approach reduces the overall development costs by ensuring these expensive drugs are given to the right patients in the right dose to be effective.

Conclusions

Theragnostics owing to its ability to facilitate personalized treatments will become a major part of patient management in the future. It has demonstrated advantages in initial diagnosis, to patient stratification and development of treatment protocols including dose determination and drug selection as well as which radionuclide will be optimal for therapy. Further advances in target development, radionuclide production and availability, automation and drug synthesis are enabling wide spread utilization of the theragnostic approach to even remote areas. This combined with the improved quality of life for these patients and reduction in drug development costs and cost savings derived from patient selection show the economic benefit of theragnostics highlighted by the recent interest by both large pharmaceutical companies and startups in both the development and acquisition of these agents. Probably its biggest benefit is the tools it provides physicians to more accurately manage patients and their quality of life.

References

1. Rudin M, Weissleder R: Molecular imaging in drug discovery and development. Nat Rev 2:123-131, 2003
2. Alzahrani AS, Bakheet S, Mandil MA, et al: 123I isotope as a diagnostic agent in the follow-up of patients with differentiated thyroid cancer: Comparison with post 131I therapy whole body scanning. J Clin Endocrinol Metab 86:5294-5300, 2001
3. Teng FF, Meng X, Sun XD, et al: New strategy for monitoring targeted therapy: Molecular imaging. Int J Nanomed 8:3703-3713, 2013
4. Gerber DE: Targeted therapies: A new generation of cancer treatments. Am Fam Physician 77:311-319, 2008
5. Fleuren EDG, Versleijen-Jonkers YMH, Heskamp S, et al: Theranostic applications of antibodies in oncology. Mol Oncol 8:799-812, 2014
6. Kenny GE, Dunsmoor CL: Principles, problems and strategies in the use of antigenic mixtures for the enzyme-linked immunosorbent assay. J Clin Microbiol 17:655-665, 1983
7. Brown M, Wittwer C: Flow cytometry: Principles and clinical applications in hematology. Clin Chem 46:1221-1226, 2000
8. Grillo-López AJ: Zevalin: The first radioimmunotherapy approved for the treatment of lymphoma. Expert Rev Anticancer Ther 2:485-493, 2002. https://doi.org/10.1586/14737140.2.5.485
9. Srinivasan A, Mukherji SK: Tositumomab and I-31-tositumobab (Bexxar). 32:637-638, 2011. https://doi.org/10.3174/ajnr.A2593
10. Nowakowski GS, Witzig TE: Radioimmunotherapy for B-cell non-Hodgkin lymphoma. Clin Adv Hematol Oncol 4:225-231, 2006
11. Lamberts SWJ, Barker WH, Reubi J-C, et al: Somatostatin-receptor imaging in the localization of endocrine tumors. N Engl J Med 323:1246-1249, 1990
12. Graham MM, Menda Y: Radiopeptide imaging and therapy in the United States. J Nucl Med 52(Suppl 2):56S-63S, 2011
13. Krenning EP, Kwekkeboom DJ, Bakker WH, et al: Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: The Rotterdam experience with more than 1000 patients. Eur J Nucl Med 20:716-731, 1993
14. Valkerma R, de Jong M, Bakker WH, et al: Phase 1 study of peptide receptor radionuclide therapy with [In-DTPA]ocreotide: The Rotterdam experience. Semin Nucl Med 32:110-122, 2002
15. Albert R, Smith-Jones P, Stolz B, et al: Direct synthesis of [DOTA-DPhe1]-octreotide and [DOTA-DPhe1,Tyr3]-octreotide(SMT487): Two conjugates for systemic delivery of radiotherapeutic nuclides to somatostatin receptor positive tumors in man. Biorg Med Chem Lett 8:1207-1210, 1998
16. Jamar F, Barone R, Mathieu S, et al: 86Y-DOTA-D-Phe1-Tyr3-octreotide (SMT487) — a Phase 1 clinical study: Pharmacokinetics, biodistribution and renal protective effect of different regimes of amino acid co-infusion. Eur J Nucl Med Mol Imaging 30:510-518, 2003
17. Barone R, Borson-Chazot F, Valkerma R, et al: Patient-specific dosimetry in predicting renal toxicity with 90Y-DOTATOC: Relevance of kidney volume and dose rate in finding a dose-effect relationship. J Nucl Med 46:995-1065, 2005
18. Delaloye AB: Highlights of the annual meeting of the European Association of Nuclear Medicine: Copenhagen 1996. Eur J Nucl Med 24:219-232, 1997
19. Dennis-Beron S: The role on theragnostics in oncology: An interview with Stefano Buono. Int J Endo Oncol 4:121-125, 2017
20. Morris MJ, Divgi CR, Pandit-Tasker N, et al: Pilot trial of unlabeled and indium-111 labeled anti-prostate-specific membrane antigen antibody J591 for castrate metastatic prostate cancer. Clin Cancer Res 11:7454-7461, 2005
21. Vallabhajosula S, Kiji I, Hamacher KA, et al: Pharmacokinetics and biodistribution of ^{111}In and ^{177}Lu-labeled J591 antibody specific for prostate-specific membrane antigen: Prediction of ^{90}Y-J591 radiation dosimetry based on ^{111}In or ^{177}Lu? J Nucl Med 46:634-641, 2005
22. Tagawa ST, Milowsky MI, Morris M, et al: Phase II study of lutetium-177 labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. Clin Cancer Res 19:1869-1875, 2013
23. Kawano MOJ, Vallabhajosula S, Tagawa S, et al: ^{111}In-J591 scan to predict PSMA targeting and treatment response following RIT with ^{177}Lu-J591 monoclonal antibody in patients with metastatic prostate cancer. J Nucl Med 51(suppl. 2), 2010. Abstract no. 173
24. Vallabhajosula S, Goldsmith SJ, Kostakoglu L, et al: Radioimmunotherapy of prostate cancer using ^{90}Y- and ^{177}Lu-labeled J591 monoclonal antibodies: Effect of multiple treatments on myelotoxicity. Clin Cancer Res 11:719s-7200s, 2005
25. Afshar-Oromieh A, Avtzi E, Giesel FL, et al: The diagnostic value of PET/CT imaging with the ^{68}Ga-labeleed PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 42:197-209, 2015
26. Benesova M, Schafer M, Bauder-Wust U, et al: Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. J Nucl Med 56:914-920, 2015
27. Beneslova M, Bander-Wust U, Schafer M, et al: Linker modification strategies to control the prostate-specific membrane antigen (PSMA)-targeting and pharmacokinetics properties of DOTA-conjugated PSMA inhibitors. J Med Chem 59:1761-1775, 2016
28. Kratochwil C, Bruchertseifer F, Giesel FL, et al: ^{225}Ac-PSMA-617 for PSMA-targeted α-radiation therapy of metastatic castration-resistant prostate cancer. J Nucl Med 57:1941-1944, 2016
29. Delkar A, Fendler AP, Krathochwil C, et al: Dosimetry for ^{177}Lu-DKFZ-PSMA-717: A new radiopharmaceutical for the treatment of metastatic prostate cancer. Eur J Nucl Med Mol Imaging 43:42-51, 2016