2017 SNMMI Highlights Lecture: Oncology

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From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and presented for more than 30 years by Henry N. Wagner, Jr., MD. Beginning in 2010, the duties of summarizing selected significant presentations at the meeting were divided annually among 4 distinguished nuclear and molecular medicine subject matter experts. Each year Newsline publishes these lectures and selected images. The 2017 Highlights Lectures were delivered on June 14 at the SNMMI Annual Meeting in Denver, CO. In this issue we feature the first part of the lecture by Wolfgang Weber, MD, a professor and chief of the Molecular Imaging and Medicine Service at the Memorial Sloan Kettering Cancer Center (New York, NY), who spoke on highlights in oncology. The second part will appear in the February 2018 (next) issue of Newsline. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine (2017;58 [suppl 1]).

A s always oncology was a major topic at this year’s SNMMI Annual Meeting, accounting for the largest number of abstracts presented. Time limitations prevent me from including in this lecture all of the excellent studies for which authors so generously sent slides.

Oncology as represented at the SNMMI 2017 meeting was truly international, with a total of 444 presentations organized into 16 topic tracks. The distribution of submissions from North America (144), Asia (142), and Europe (116) was fairly equal, with additional abstracts from the Middle East (18), South America (10), Australia (8), and Africa (6). We are seeing a striking increase in the number of abstracts related to nuclear therapies, even on a year-to-year basis from 2016 to 2017. Perhaps more interesting is the fact that when the top 20% of abstracts are considered, a third were related to therapy rather than diagnosis of cancer. In terms of diseases studied, prostate cancer and genitourinary foci dominated with 97 abstracts, compared to lymphoma/myeloma/leukemia (42), lung (38), colorectal and liver (30), breast (23), sarcoma/melanoma (18), head and neck (17), gynecologic (14), and other (151) studies. Again, if only the highest ranking 20% of abstracts are considered, about a third were related to prostate cancer. Many tracers were reported on at the meeting, with FDG, prostate-specific membrane antigen (PSMA), choline, and fluoride agents accounting for somewhat less than half, and other agents, including innovative experimental and therapeutic compounds, accounting for the rest. When looking at only the top 20% of abstracts, however, PSMA-based tracers accounted for almost a fourth of the total.

I offer these aspects of the aggregate presentations not only to provide an overview on where the field of nuclear medicine and molecular imaging in oncology is headed but also to explain why such a large portion of my lecture will focus on PSMA imaging.

Prostate Cancer and PSMA

Most attendees here are aware of PSMA, but a brief introduction is in order. PSMA is an enzyme, glutamate carboxypeptidase (also known as GCPII), that is highly expressed in primary and metastatic prostate cancer. It is important to remember that PSMA is also expressed in many normal tissues, including the proximal tubules of the kidney, the jejunal brush border of the small intestine, and the ganglia of the nervous system. It is also found in the vasculature of several types of tumors. Although it is probably too late now, in retrospect it would have been more accurate to routinely refer to this enzyme with a more inclusive name than “prostate specific.” In fact, what we refer to as PSMA is termed N-acetyl-L-aspartyl-L-glutamate peptidase I by neuroscientists and folate hydrolase by those studying folate metabolism.

Burger et al. from University Hospital Zurich (Switzerland) reported that “PET/MR further improves detection of 68Ga-PSMA-11 imaging for early biochemical recurrence in prostate cancer” [709]. I selected this study for presentation out of many abstracts in this category for 2 reasons. The authors used time-of-flight (TOF) PET/MR imaging in patients with elevated prostate-specific antigen (PSA) levels after treatment of prostate cancer as part of a protocol that required only 30 minutes. This is a major achievement, because long acquisition times currently constitute a major challenge to routine clinical use of PET/MR. The ability to perform a 30-minute protocol that enables both pelvic and whole-body imaging is important for the future of the field. The authors also focused in on patients with low PSA levels (0.2–0.5 ng/mL), a group in whom a 72.7% detection rate was achieved with this shorter imaging protocol. Figure 1 shows the very tiny lymph nodes that were positive on PET and could be correlated with MR results. The authors concluded that “68Ga-PSMA TOF PET/MR imaging might further improve the detection rate in early biochemical recurrence compared to published data for 68Ga-PSMA-11 PET imaging,” adding that even at very low PSA levels of <0.5 ng/mL, extrapelvic disease could be localized in 25% of patients. PET/MR imaging with this TOF scanner system shows
clear promise for detection of metastatic prostate cancer at a very early stage.

Roach, from Royal North Shore Hospital (Sydney, Australia), and colleagues from the Australasian Radio-pharmaceutical Trials Network and research centers across Australia, reported on “Australian prospective multicentre evaluation of clinical management intent utilising 68Ga-PSMA PET/CT scans in patients with prostate cancer” [2409]. 68Ga-PSMA-11 has now been used around the world in several large series of patients. This consortium of researchers looked at data from 431 patients and reported that the use of 68Ga-PSMA resulted in a change in planned management in 51%, a significant result. This change was found to be even higher (at 62%) in the group with biochemical recurrence (with disease found to be more extensive in 51% and less extensive in 10%). In primary staging of intermediate- and high-risk disease, the change in planned management was lower but still significant at 21% (with disease found to be more extensive in almost all of those with management changes). This shows not only that PSMA imaging has an impact on management of prostate cancer but that this impact depends on the context of the disease, so that we should be cautious in generalizing about PSMA agents in prostate cancer and, instead, specifically define the context of use.

The broad use of PSMA has also shown that it is not entirely specific for prostate cancer. Osman et al. from St. Louis University (MO) and the Peter MacCallum Cancer Institute (Ripponlea and East Melbourne, Australia) reported on “Detection of unexpected additional primary malignancies with 68Ga-PSMA PET/CT in patients with prostate cancer: Frequency in 765 patients” [736]. Figure 2 shows 68Ga-PSMA-11 PET/CT images of squamous cell carcinomas, unrelated to prostate cancer, that were highly PSMA-11 avid. These authors reported that synchronous PSMA-avid malignancies are rare (0.7%) in patients with prostate cancer, with atypical lesions usually representing unusual prostate cancer metastases or benign lesions. However, their results emphasize that although PSMA is an enzyme expressed predominantly in prostate cancer, it is important to remember that it is not prostate cancer–specific but expressed in other tumors. The authors cautioned that “in cases with unexpected 68Ga-PSMA-11 PET/CT findings, further clarification with close follow-up, other imaging modalities, or pathological confirmation is critical.”

We should also remain aware that PSMA is taken up in nonmalignant lesions and tissues. Keidar et al. from Rambam Health Care Campus (Haifa, Israel) and Chaim Sheba Medical Center (Tel Hashomer, Israel) reported on “68Ga-PSMA-11 PET/CT in prostate cancer patients—normal variants and pitfalls” [1085]. In a retrospective review of 68Ga-PSMA-11 PET/CT studies in 148 men (mean age, 71.5 years; range, 56–89 years) with prostate cancer, the authors identified 49 nonmalignant findings in a total of 43 studies (accounting for 29% of the total population studied). Just as with FDG, we need to remember that not every focal uptake of PSMA means cancer, although in general the specificity is quite good. Figure 3 is an example of a benign thyroid nodule that showed intense 68Ga uptake. The authors concluded that “knowledge of increased tracer uptake in sites unrelated to prostate cancer involvement is important in order to avoid potential pitfalls in accurate interpretation of 68Ga-PSMA-11 PET/CT studies.”

The success of 68Ga-PSMA-11 has also stimulated new research into creating different tracers for prostate cancer. The most obvious approach is to look for an alternative radionuclide, because the supply of 68Ga is relatively limited...
by the availability of generators. $^{18}$F is a logical choice for exploration in PSMA labeling, given its availability and long-standing dominance in our field. Giesel et al. from the University of Heidelberg and the German Cancer Research Center (DFKZ) (both in Heidelberg, Germany) reported on “Intra-individual comparison of $^{18}$F-labeled PSMA-1007 PET/CT, multiparametric MRI, and radical prostatectomy specimen in patients with primary prostate cancer” [539]. Figure 4 is an example from their presentation on the utility of the tracer in staging local disease in primary prostate cancer. They showed a close correlation between uptake of this $^{18}$F-labeled compound and tumor location at histology. Although in the case shown in Figure 4 the tumor is also visible in the MR images, it is clear that the PET image is much easier to read. Not only is the high sensitivity of this PET tracer promising, but interpretation may be much more straightforward than with multiparametric MR scans. The authors concluded that a combination of $^{18}$F-PSMA-1007 PET/CT multiparametric MR imaging may be ideal for detection and local staging in prostate cancer.

The same group of researchers presented additional studies with this tracer at this meeting. Freitag et al. from the German Cancer Research Center (DFKZ) and the University of Heidelberg (both in Heidelberg, Germany) reported on “Simultaneous whole-body $^{18}$F-PSMA-1007 PET/MRI with integrated multiparametric MRI of the prostatic fossa for comprehensive oncological staging of patients with prostate cancer” [538]. Figure 5 shows a patient with multiple lymph node metastases. Of special note is that, in contrast to most of the other PSMA ligands, this agent is not excreted via the bladder. The image shows the fluid-filled bladder with no excretion of the tracer; uptake is visible only in the prostate cancer. This could be a significant advantage for imaging in prostate cancer, where $^{68}$Ga activity in the urine can be a confounding factor. These authors focused on the complementarity of PET and MR in this setting: “the combination of optimal pharmacodynamics of $^{18}$F-PSMA-1007 (low bladder signal) and the PI-RADS 2.0-compliant MRI protocol being standard for assessment of primary prostate cancer represent an optimal synergy of molecular and radiological assessment by exploiting the strengths of both to overcome limitations that each modality may have.”

Khawar et al. from the Universitätsklinikum (Bonn, Germany) and the Johannes Gutenberg University (Mainz, Germany) reported on “Biodistribution and dosimetry with $^{44}$Sc-PSMA-617: First results” [2093]. $^{44}$Sc has a longer half-life than $^{18}$F and $^{68}$Ga and therefore allows imaging later after injection of the radiotracer. This may increase contrast and, perhaps more important, may facilitate accurate prediction of radiation dose for radionuclide therapy with PSMA-targeted treatments. The authors performed a first-in-human study with this compound and reported on radiation exposure of normal organs, with results indicating effective doses comparable to those of $^{68}$Ga-PSMA-617.
They concluded that $^{44}$Sc-PSMA-617 may prove to be better for pretherapeutic dosimetry for $^{177}$Lu-PSMA-617 endoradiotherapy. This is a promising tracer for the future, especially in patients being considered for radionuclide therapy with a PSMA-targeting agent.

In addition to applications in PET and SPECT, researchers are interested in potential uses of PSMA in intraoperative imaging. Differentiation between tumor and normal tissues is often quite difficult in prostate surgery, and it is especially challenging to find those tiny lymph nodes that we can visualize on PSMA PET scans. The availability of a PSMA imaging agent that can be combined with fluorescence imaging is therefore of significant interest. Baranski et al. from the German Cancer Research Center (DFKZ) and the University of Heidelberg (both in Heidelberg, Germany) reported on “Preclinical evaluation of dual-labeled PSMA inhibitors for the diagnosis and therapy of prostate cancer” [531]. In this research, $^{68}$Ga-PSMA-11 was conjugated with a fluorescent dye (IRDye800CW) and applied in tumor uptake and pharmacokinetic studies in LNCaP tumor-bearing mice and healthy pigs. The purpose of such dual-modality compounds is first to enable PET imaging, to ascertain the approximate locations of the lymph node metastases, followed by intraoperative gamma camera imaging to allow the surgeon to better localize the site(s) of disease. Then intraoperative fluorescence imaging can be applied to ensure that the right lymph node(s) has been extracted and that the resection is complete. One very interesting aspect of this work is that this dual tracer can be used not only for the macroscopic fluorescence imaging we associate with intraoperative procedures but also to identify on the microscopic or cellular level the locations at which this imaging agent binds. The result means that we will be able for the first time to follow the PET signal to the cellular and subcellular binding sites where a new tracer accumulates. It is true that efforts have been underway for a number of years to design effective dual-modality agents. However, many of these approaches failed because as the affinity decreased, the tumor uptake also decreased and biodistribution became less favorable. Remarkably, for the compound investigated in this presentation, this was not the case. In fact, tumor uptake of this dual-modality agent was higher than that of either single-modality agent. This is a promising compound for translation into humans, especially in studies designed to determine whether it can be used to guide treatment of prostate cancer from the macroscopic to the truly microscopic level. Figure 6 is an example showing both intraoperative imaging in a pig, with the physiologic expression clearly visualized in the prostate, and the fluorescent signal in the tumor model in a mouse, with corresponding PET images.

Despite the success of and well-justified excitement about PSMA as an imaging and therapeutic target, I believe that prostate cancer is such a heterogeneous disease entity that we cannot say that PSMA is a final answer to all questions about prostate cancer imaging and therapy with radionuclides. Evidence of this is seen in presentations at this meeting that looked at other targets. Zhang et al. from Peking Union Medical College Hospital (Beijing, China) and the National Institutes of Health (Bethesda, MD) reported on “Clinical translation of gastrin-releasing peptide receptor (GRPR) antagonist $^{68}$Ga-NOTA-RM26 in healthy volunteers and prostate cancer patients” [384]. In this first-in-human study, the researchers demonstrated that this agent, similar to the PSMA-targeting molecule, shows high uptake in primary tumor and also osseous metastases. They also showed a close correlation of the expression of this target in tissue, as documented by staining on immunohistochemistry, and the intensity of uptake on PET imaging (Fig. 7). These promising data warrant future studies that ask the question whether targeting both PSMA and GRPR is superior to targeting PSMA. A similar agent, $^{68}$Ga-RM2, is a GRPR antagonist that binds to the same target. Harrison et al. from Stanford University (CA) reported on “Detection of recurrent prostate cancer using $^{68}$Ga-RM2 PET/MRI in patients with negative conventional imaging” [711]. Their results in a study with 31 patients showed that $^{68}$Ga-RM2 PET is promising in this setting. Figure 8 is an example of a very small subcapsular liver implant detected by this agent. It is noteworthy that this was probably only detectable because hepatic uptake with this tracer was quite low, in marked contrast to PSMA agents. This is a reminder that not only is tumor uptake important to assess in different compounds but that differences in normal distribution may be significant. This is another reason to explore different compounds and not focus solely on one.

**Radionuclide Therapy**

Our focus will now shift from imaging applications to therapeutic applications in prostate cancer and other
diseases (although, again, the presentations at this year’s meeting were heavily weighted toward prostate cancer).

At last year’s meeting, the results of the neuroendocrine tumor (NET) therapy NETTER-1 trial were presented and demonstrated for the first time in a randomized setting that radionuclide therapy targeting somatostatin receptor type-2 can significantly improve outcomes for patients with metastatic NETs. At this year’s meeting, Strosberg, from the Moffatt Cancer Center (Tampa, FL), and the group running the NETTER-1 trial reported that “NETTER-1 phase III trial suggests quality of life improvements in patients with midgut neuroendocrine tumors” [244]. It is important to remember that this trial compared radionuclide therapy (177Lu-DOTATATE) with one of the most benign treatments in oncology (octreotide). It is quite interesting that, despite the fact that the comparison arm had a very low frequency of side effects, treatment with the radionuclide actually made patients feel better and feel better earlier in the course of treatment. Over the course of the 72 weeks of the study, 28% of patients in the 177Lu-DOTATATE and 15% of patients in the octreotide arm saw global health status improve. Over the same period, 18% of patients in the 177Lu-DOTATATE and 26% of patients in the octreotide arm saw global health status worsen. The largest statistical differences between the arms were seen between 24 and 48 weeks. At most of the time points in the study, patients actually felt better when they were treated with the radioactive compound—illustrating that one strength of many of these targeted radionuclide therapies is that they have few side effects.

Many therapeutic applications of radiolabeled PSMA agents are currently under investigation. It is encouraging that this work comes not from one country alone but from many countries around the world. Yadav et al. from the All India Institute of Medical Sciences (New Delhi) and New Delhi NCR (both in India) reported on “177Lu-DKFZ-PSMA-617 therapy in metastatic castration-resistant prostate cancer: Safety, efficacy, and quality of life assessment” [314]. This study confirmed that this treatment approach can be quite effective, as shown in Figure 9, an example of a patient who achieved complete response after 3 cycles of treatment. The overall biochemical response rate in this patient population was 59%.

Despite these successes and the fact that these studies are now ongoing around the world, we still know very little about this treatment. There is room for many more systematic studies, and these could focus on a series of key questions that must be answered. One set of questions, for example, is: How many cycles should we administer, and
when should we decide whether to continue a treatment or stop treatment? Rahbar et al. from University Hospital Munster and University Hospital Bonn (both in Germany) reported on “Antitumor activity of repeated $^{177}$Lu-PSMA-617 radioligand therapy in patients with metastatic castration-resistant prostate cancer” [315]. Much like the study from India just cited, these authors found that the chemical response rate was 56% in their patient population and that in 66% of patients there was some decrease in PSA. What was novel in this report was that this decrease in PSA did not necessarily occur after the first cycle of treatment. In a significant fraction of patients this decrease occurred only after the second cycle or later. The authors concluded that decisions about continuing or curtailing the treatment should not be made after the first cycle but should be reserved until after the second cycle or later.

Another key question is: What is the right dose of $^{177}$Lu to be useful in treatment? It is important to have evidence-based data to know whether the standard dose is the right one or whether it should be escalated or lowered. Surprisingly little information is available to support such decisions. Rathke et al. from University Hospital Heidelberg and the University of Heidelberg (Germany) reported on “Dose escalation of $^{177}$Lu-PSMA-617 from 4 to 9.3 GBq per cycle in patients with metastatic castration-resistant prostate cancer” [313]. Their retrospective study detailed clinical observations in 40 patients treated with different activities of the radionuclide. All patients had advanced prostate cancer and evident disease on PSMA imaging. At the lowest dose (4 GBq), 8 of 10 patients did not have a sufficient response, whereas only 4 of 10 had an insufficient response at the highest dose (9.3 GBq). At this dose, however, toxicity/side effects increased but were still manageable. This indicates that we can probably increase to a higher dosage per treatment but must be aware that this treatment may have more hematologic side effects than we see now. Again, this should be balanced against the potential benefits.

Yet another key question is: How frequently should we administer this treatment? Typical cycles are currently every 8 weeks, but, again, not much data support this periodicity or explain why 4 or 6 weeks might be better or worse. Haug et al. from the Medical University of Vienna, Chmed Vienna, and the Ludwig Boltzmann Institute for Applied Diagnostics (all in Vienna, Austria) reported on “Efficacy and toxicity of an aggressive treatment schedule of metastatic prostate cancer using 3 cycles of 7.4 GBq $^{177}$Lu-PSMA DKFZ-617 every 4 weeks” [318]. In almost all of 26 patients they showed an impressive decrease in PSA. Figure 10 is an example of tumor response to this treatment. Overall survival was also quite encouraging, with remarkable median profession-free survival at 46 weeks. The rate of serious toxicities was quite low, despite the fact that the treatment was administered at twice the usual frequency. The authors concluded that because their results were safe and effective, as well as comparable or favorable to conventional $^{177}$Lu-PSMA DKFZ 617 schedules, that “treatment with high doses every 4 weeks might better reflect the more aggressive nature of castration-resistant metastatic prostate cancer.”
A final question is: Should we always give the same amount of $^{177}\text{Lu}$ for every cycle? Although this is now the standard approach, it is reasonable to ask whether advantages might accrue to administering different amounts of radioactivity at different treatment cycles. Kulkarni et al. from the Zentralklinik Bad Berka (Germany) reported on “Serial dosimetry during $^{177}\text{Lu}$-PSMA radioligand therapy in the same patient” [316]. The authors performed dosimetry, imaging, and other analyses at each cycle of therapy (Fig. 11). All dosimetric parameters pertaining to metastases showed a reduction between the first and second therapy cycles: uptake declined by 57%, residence time by 62%, and dose by 64%. In contrast, the renal uptake increased by 62% and the residence time was 34% higher at the second cycle. The mean renal dose was therefore higher in the following cycles (34%). The authors emphasized the importance of performing individual dosimetry at the first and at least the second cycle. These results require further study to understand the mechanisms at work but also suggest that we may want to adjust the amount of $^{177}\text{Lu}$ administered from cycle to cycle.

This highlights lecture will be continued in the February issue of Newsline.

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**The First Theranostic Conference at the American University of Beirut Medical Center**

*Hossein Jadvar, MD, PhD, MPH, MBA, Past SNMMI President*

Nuclear medicine is gaining strength across the world. One of the major strategic goals of the SNMMI has been to support our international membership and activities. The First American University of Beirut Medical Center (AUBMC) Theranostics Conference was held in Lebanon on November 10–11, with the theme “See What You Treat.” I was privileged to participate, along with my colleagues Homer Macapinlac, MD (MD Anderson Cancer Center; Houston, TX), Medhat Osman, MD (St. Louis University; MO), Partha Choudhary, MD (Rajiv Gandhi Cancer Institute; Delhi, India), and Diana Paez, MD (International Atomic Energy Agency [IAEA]; Vienna, Austria). The meeting was organized by the AUBMC Division of Nuclear Medicine, Department of Diagnostic Radiology, and led by Mohammad B. Haidar, MD. The IAEA endorsed the 2-day conference, which was designed to highlight research and clinical work in theranostics, focusing on current capabilities and the future outlook in Lebanon and the Middle East. The conference also included local nonimaging clinical specialists (e.g., urologists, medical oncologists, radiation oncologists, and surgeons), who actively participated in discussions on the utility and limitations of imaging in various clinical settings. On the cultural side, we had a brief opportunity to visit a few of the major sites within the beautiful city of Beirut and enjoy authentic Lebanese cuisine. I hope that more such local engagements will be held across the world to promote nuclear medicine and molecular imaging.
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