2015 SNMMI Highlights Lecture: Oncology, Part II

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From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and delivered 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. The 2015 Highlights Lectures were delivered on June 10 at the SNMMI Annual Meeting in Baltimore, MD. Umar Mahmood, MD, PhD, Professor of Radiology at Massachusetts General Hospital (Boston, MA), spoke on oncology highlights from the meeting’s sessions. Because of its length, the oncology presentation is divided between 2 Newsline issues. Part I was published in the November issue. Note that in the following summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine [2015;56:suppl 3].

At this year’s SNMMI Annual Meeting we have seen interesting work with growing numbers of tracers—both novel agents and innovative applications for tracers that are already familiar. One example is in hepatocellular cancer (HCC), where grades B and C carcinoma (intermediate grades) may be treated with 90Y-selective internal radiation therapy (90Y-SIRT). The predictive role of pretreatment 18F-FDG PET/CT in 90Y-SIRT for inoperable HCC patients with 18F-FDG–avid tumors is well documented. However, it is not well studied in HCC cases that are non-avid, because these lesions may also include non-HCC cirrhotic nodules lumped together as a single “18F-FDG–non-avid” category by others. Chen et al. from the Hong Kong Sanatorium and Hospital reported that 11C-acetate PET/CT predicts treatment response and survival of cohort of Barcelona Clinic Liver Cancer B-C patients treated with 90Y-SIRT” [573]. These researchers looked at the value of 11C-acetate and 18F-FDG PET/CT for prediction of treatment efficacy and posttreatment survival in 18 patients referred for imaging within 2 weeks before 90Y-SIRT. PET/CT with both tracers was performed at 2 months after treatment. On pretreatment imaging, 8 patients showed 11C-acetate avidity and 10 showed 18F-FDG avidity. All 8 (100%) of the patients with 11C-acetate avidity proved to be good responders to treatment, whereas only 5 (50%) with 18F-FDG avidity had good responses. Metabolic poor/good response as assessed on follow-up PET/CT was a significant predictor for 2-year overall survival in these patients. Figure 1 shows examples from this study. On the left are follow-up (top) and baseline (bottom) 18F-FDG and 11C-acetate images from a patient with 11C-acetate–avid HCC who went on to a good treatment response, with survival >24 months. On the right are corresponding images from a patient with 18F-FDG–avid HCC but without 11C-acetate avidity who died 9 months after treatment. Whether a tumor is more fatty acid dependent or glucose dependent may help to characterize its genetic makeup or its phenotype and inform subsequent treatment strategies.

Brain tumors can be assessed in many ways, and a recent body of exciting work looks at the potential of amino acid imaging. One of the challenges in brain metastasis imaging is in differentiating tumor recurrence from radiation necrosis. Guffens et al. from Universitaire Ziekenhuizen Leuven–Katholieke Universiteit Leuven (Belgium) reported that “Dynamic O-(2-18F-fluoroethyl)-L-tyrosine (18F-FET) PET improves differentiation of local recurrent brain metastasis from radiation necrosis” [628]. Only limited data are available on the value of dynamic 18F-FET PET in such differentiation. In this retrospective analysis, the researchers looked at 29 patients (39 lesions) previously treated with stereotactic radiation surgery or whole-brain radiation therapy for brain metastasis who currently had at least 1 contrast-enhancing lesion on MR imaging. All patients underwent 18F-FET PET imaging, and the results were classified by kinetic uptake patterns as: pattern 1, constantly increasing time–activity curve (TAC); pattern 2, stable TAC, early peak (<20 minutes after injection) followed by plateau; and pattern 3, decreasing TAC, early peak (<20 minutes after injection) followed by decrease. For analysis, patterns 2 and 3 were grouped together and compared with pattern 1. Histology and follow-up determined that 32 lesions (82%) were recurrent metastases and 7 (18%) represented radiation necrosis. The researchers showed that accuracy for correct identification of recurrent brain metastases was only 54% using static tumor-to-background ratios (TBRs). This percentage rose to 72% for TAC patterns 2 and 3 compared with TAC pattern 1. The authors achieved 100% specificity when TBR was >2.37 in lesions categorized as patterns 2 or 3. However, combining TBR and uptake patterns did not improve diagnostic accuracy. Although these are promising data, it is clear that there is room for more work with other tracers and/or approaches in the setting of differentiating brain metastases from necrosis.

Another interesting target in cancer is the α-chemokine receptor CXCR4. Wang et al. from the Fourth Military Medical Hospital (Xi’an, China) and the National Institute of Biomedical Imaging and Bioengineering (Bethesda, MD) reported on a “Prospective study of 68Ga-NOTA-NFB: radiation dosimetry in healthy volunteers and first application
CXCR4 is overexpressed in various types of human cancer. As a specific imaging agent for CXCR4, $^{68}$Ga-NOTA-NFB was investigated to assess its safety, biodistribution, and dosimetric properties in 6 healthy volunteers and to preliminarily evaluate its application in 8 patients with glioma. Figure 2 shows a comparison of MR (top), $^{18}$F-FDG PET (middle), and $^{68}$Ga-NOTA-NFB PET (bottom) imaging in 3 patients with (left to right) grades 2, 3, and 4 glioma. In grade 2 glioma, where there is not a blood–brain barrier breakdown, no uptake is seen, which may be a reflection of delivery. Images from grades 3 and 4 clearly show that CXCR4 expression is targeted by $^{68}$Ga-NOTA-NFB. This tracer has the potential not only for use in initial detection and tumor assessment but for in situ tumor characterization of changes and to help guide therapy and responsiveness. Many of our new tracers have these multilevel goals: to provide not only better diagnosis, staging, and monitoring but also useful characterization of tumors in situ.

Lapa et al. from Würzburg University (Germany) and the Technische Universität München (Germany) reported on “First in man experience of CXCR4-directed endoradiotherapy with $^{177}$Lu- and $^{90}$Y-labeled pentixafor in multiple myeloma patients” [14]. The group used their CXCR4 ligand not only for imaging but also for radiotherapy. The group has previously reported on $^{68}$Ga-pentixafor (pentixafor) in a number of human malignancies, including lymphoma, chronic lymphocytic leukemia, and multiple myeloma. In multiple myeloma, $^{68}$Ga-pentixafor for PET has shown encouraging results in comparison to $^{18}$F-FDG PET, including identification of patients for CXCR4-directed treatment and peptide receptor radiotherapy (PRRT). Development of derivatives of the group’s original compound allowed labeling with a range of $\alpha$ and $\beta$ emitters. Their theranostic approach used 2 $\beta$ emitters: $^{177}$Lu and $^{90}$Y. Figure 3 shows encouraging responses in 2 patients. Before $^{177}$Lu-pentixafor treatment, patient 1 (left) showed sites of CXCR4 expression and uptake on $^{68}$Ga-pentixafor, correlating well with uptake on $^{18}$F-FDG (next right), which indicated numerous osseous sites involved. Two weeks after $^{177}$Lu-pentixafor administration $^{18}$F-FDG PET showed a good partial response. In the second patient (right), pretreatment imaging showed overexpression of CXCR4 before therapy, correlating reasonably well with $^{18}$F-FDG uptake, with a complete response after $^{177}$Lu-pentixafor treatment. The authors concluded that, in combination with high-dose chemotherapy and autologous stem cell transplantation, CXCR4-targeted PRRT with pentixafor is a promising new option for patients with advanced multiple myeloma. We are rapidly expanding our armamentarium of theranostic agents. We began with iodine, the historical mainstay of nuclear medicine, and we have had excellent work with somatostatin receptors as well as prostate-specific membrane antigens (PSMAs). This paper and others at the Annual Meeting made it clear that...
vigorous investigations are underway in other cancers and other agents to explore the potential of combined theranostics. Another study from Chen et al. from Hong Kong Sanatorium and Hospital and the University of Hong Kong, this one looking at myeloma and at the prognostic value of imaging, reported that “\(^{11}\)C-acetate PET/CT predicts 4-year overall survival for patients with newly diagnosed myeloma” [657]. In a population of 20 patients with multiple myeloma (13 stage I, 3 stage II, 4 stage III by the International Staging System), \(^{11}\)C-acetate PET/CT was positive in 18 (90%) and \(^{18}\)F-FDG was positive in 12 (60%). During 4 years of follow-up, 8 (40%) patients died. Subsequent analysis identified 2 significant predictors of overall survival: pretreatment generalized marrow activity (maximum standardized uptake value \([SUV_{\text{max}}]\) on L3) assessed by \(^{11}\)C-acetate PET/CT and pretreatment serum \(\beta\)-2 microglobulin levels. Patients with diffuse uptake at baseline had much poorer outcomes than patients who had less uptake in the marrow. Figure 4 shows example images from 2 patients, with \(^{11}\)C-acetate PET images on the left in each set and \(^{18}\)F-FDG PET images on the right. For the patient on the left, L3-measured generalized marrow activity was 5.6 for \(^{11}\)C-acetate and 2.7 for \(^{18}\)F-FDG PET. This patient survived for 27 months. L3-measured generalized marrow activity was 3.6 for \(^{11}\)C-acetate and 2.7 for \(^{18}\)F-FDG PET in the patient on the right, for whom survival was \(>4\) years. \(^{18}\)F-FDG uptake was the same in these patients, but \(^{11}\)C-acetate appeared to correlate with outcome in these representative examples.

Much recent work has focused on theranostic applications based on PSMA as a target. Kulkarni et al. from the Zentralklinik Bad Berka (Germany) and Technische Universität München (Germany) reported on “Therapy of metastasized castrate-resistant prostate cancer using \(^{177}\)Lu-labeled DOTAGA-PSMA small molecules: first clinical results in a larger patient cohort” [10]. Figure 5 shows patients with diffuse metastases who have responded well to \(^{177}\)Lu therapy. \(^{177}\)Lu can be directly imaged with SPECT/CT to monitor tumor dose delivery. In this safety and efficacy study, the researchers reported on \(^{177}\)Lu-PSMA therapy results in 60 patients with a total of 142 cycles (2–5 per patient), a mean administered radioactivity of 8.7 GBq per cycle, and a mean follow-up of 12 months (range, 3–25 months). Response was measured according to molecular response criteria on \(^{68}\)Ga-PSMA PET/CT, correlating with a fall in prostate-specific antigen (PSA) after therapy (Fig. 6). No hematologic, renal, or salivary toxicities were noted, and improvements in quality of life and pain scores were noted in all patients. After 2–4 cycles of therapy, the researchers noted 1 patient with molecular complete remission, 13 with partial remissions, 2 with stable disease, and 9 with progressive disease. Progression-free survival was 14 months, and the overall survival median was not reached over the 15 months of the study, which are exciting results in patients with these very advanced cancers. The authors concluded that peptide radio-ligand therapy using \(^{177}\)Lu-labeled DOTAGA-based PSMA small molecules is safe and effective in castrate-resistant metastatic prostate cancer and potentially may confer survival benefits when compared with conventional therapy regimens.

A number of different and new-generation PSMA-targeting agents are under investigation. Benesova et al. from the German Cancer Research Center (Heidelberg) and University Hospital Heidelberg (Germany) reported on “PSMA-617—a novel theranostic PSMA inhibitor for both diagnosis and endoradiotherapy of prostate cancer” [63]. This group has identified a theranostic PSMA inhibitor which they have labeled...
with both diagnostic and therapeutic radiometals. They described their agent, PSMA-617, and its development with respect to preclinical tumor targeting and pharmacokinetics, along with clinical diagnostic scanning with 68Ga-PSMA-617 PET/CT and results from a patient treated with 177Lu-PSMA-617. Figure 7 shows these preliminary imaging and treatment results. The 68Ga-PSMA-617 PET/CT images (left) show very high uptake in the lymph nodes, providing excellent TBRs and helping to identify small lesions. This imaging approach will also be useful in identifying those patients likely to benefit from treatment with the 177Lu-labeled agent. On the right, baseline and restaging images after 177Lu-PSMA-617 treatment show a remarkable response and decrease in uptake, correlating with a change in PSA levels. Pioneering work in coupling peptide-targeted radiotherapy with imaging for somatostatin receptors in carcinoid tumors and neuroendocrine tumors has now been transferred with extraordinary promise in prostate cancer among several different groups, and we are likely to see additional significant advances in this area in the near future.

Many approaches are possible in improving prostate cancer imaging. Pandit-Tasker et al. from Memorial Sloan-Kettering Cancer Center (New York, NY) and ImaginAb Inc. (Inglewood, CA) reported on “First-in-human 89Zr-Df-IAB2M anti-PSMA minibody in patients with metastatic prostate cancer” [400]. The study included 28 patients who underwent standard imaging (CT/MR and bone scan), 18F-FDG PET imaging, and PET imaging with various doses of 89Zr-Df-IAB2M. A total of 19 biopsies (10 soft tissue, 9 bone) were performed in 18 patients. Figure 8 shows that the novel agent identified with high TBRs more metastatic sites than 18F-FDG PET or bone scanning. In lesional detection comparisons, 89Zr-IAB2M PET, 18F-FDG PET, CT, and bone scan detected 228 (81.7%), 73 (26.2%), 148 (53.1%), and 161 (57.7%), respectively, of identified bone lesions. The figures for soft tissue lesion detection were 98 (85.9%) for 89Zr-IAB2M PET, 55 (48.2%) for 18F-FDG PET, and 75...
(65.8%) for CT. A total of 65 unique bone and 32 soft tissue sites were identified only by $^{89}$Zr-IAB2M PET. $^{89}$Zr-IAB2M PET had a high concordance (89.5%) with true-positives and true-negatives at biopsy. This again points to the fact that there are many promising approaches for assessment of prostate cancer and that there is no single “right” way to image. Multiple approaches bring new insights into both the most promising treatment strategies and to our basic understanding of various pathway targets in the disease.

Mena et al. from Johns Hopkins University/Applied Physics Laboratory (Baltimore, MD) and the University of Wisconsin (Madison) reported on “First-in-man analysis of 18F-DCFPyL, a second generation, 18F-labeled PSMA-targeted radiotracer, in patients with metastatic prostate cancer” [399]. The authors reported on initial clinical experience with this agent and compared tumor uptake with that of 18F-DCFBC, the first radiofluorinated PSMA-targeted small molecule for PET imaging of prostate cancer. Figure 9 shows high uptake over time using this new agent. The researchers documented rapid, high accumulation in primary tumor, lymph nodes, and sites of bone metastasis. Physiologic accumulation corresponded to distribution of PSMA, with relatively prompt excretion of radiotracer. The median SUV$_{max}$ of 18F-DCFPyL was 2.0 times higher than that for 18F-DCFBC for nodal disease and 13.6 times that for bony lesions. Tumor-to-liver, tumor-to-blood, and tumor-to-muscle ratios were also significantly higher with 18F-DCFPyL than with the first-generation compound. This method of targeting PSMA has the advantages of a fluorine probe and a small molecule.

**Malignancies in Women**

Grootendorst et al. from King’s College London (UK) reported on the “Clinical feasibility of intraoperative 18F-FDG Cerenkov luminescence imaging (CLI) in breast cancer surgery” [13]. As part of a clinical trial focusing on breast-conserving surgery, the authors looked at the feasibility of intraoperative CLI evaluation of tumor excision margins and sentinel lymph node (SLN) metastases. Patients were injected with 5 MBq/kg 18F-FDG 1–2 hours before surgical excision of tumor and SLNs. Tumors and SLNs were split and imaged intraoperatively with CLI immediately after excision, a procedure that required <5 minutes. Figure 10 shows an example with tumor resection margins clearly identified. No evidence of radioactive contamination was found outside the operative field. The authors also looked at radiation dose to patients, surgeons, and staff with the procedure. In the United Kingdom, surgeons could potentially perform 93 such procedures per year before exceeding the annual whole-body radiation dose constraint of 6,000 $\mu$Sv. In the United States, 1,000 procedures could potentially be performed because of the higher allowable radiation dose of 50,000 $\mu$Sv. The authors concluded that intraoperative 18F-FDG CLI is a feasible and low-risk procedure.

Wang et al. from the Massachusetts General Hospital (Boston), the Memorial Sloan–Kettering Cancer Center (New York, NY), Vanderbilt University (Nashville, TN), and Seragon Pharmaceuticals (San Diego, CA) reported...
on “Validation of target engagement using 18F-fluoroestradiol (18F-FES) PET in patients undergoing therapy with selective estrogen receptor (ER) degrader, ARN-810 (GDC-0810)” [565]. The researchers were seeking to identify when a sufficient dose of the therapeutic agent had been delivered to degrade the ER, by applying 18F-FES PET to validate ER target engagement. Thirty patients underwent baseline and intertreatment imaging. The number of 18F-FES–avid lesions on baseline ranged from 1 to >10, with SUVmax ranging from 1.5 to 17.2. All except 3 posttherapy 18F-FES scans showed complete or near complete (>90%) suppression of 18F-FES uptake to background levels, indicating that ARN-810 is effective in degrading the ER sites. Figure 11 (top) shows a patient with widespread 18F-FES–avid and ERα mutant skeletal metastases at baseline and during treatment with ARN-810. Figure 11 (bottom) shows a patient with 18F-FES–avid soft tissue metastases. This successful imaging of target engagement has promise not only for identifying patients who are more likely to respond to specific therapies but for guiding therapeutic drug dosing in individual patients.

Tsujikawa et al. from the University of Fukui (Japan) reported on “Assessment of hormone sensitivity in uterine leiomyoma patients using 18F-FES PET” [345]. In the study, 10 patients with uterine leiomyomas underwent 18F-FES PET, 18F-FDG PET, and pelvic MR imaging before treatment, as well as follow-up MR imaging after 1–6 cycles of gonadotropin-releasing hormone treatment. Pretreatment tracer uptake was compared with volume reduction after therapy. Figure 12 shows the variety of ER expression in leiomyoma, with corresponding different levels of uptake. Volume after treatment corresponded quite nicely with 18F-FES uptake. The authors concluded that pretreatment 18F-FES SUV and 18F-FES/18F-FDG ratio can be used for predicting gonadotropin-releasing hormone sensitivity in uterine leiomyoma patients before treatment and that more accurate prediction may be provided in evaluation of intramural leiomyomas.

Tade et al. from Emory University (Atlanta, GA) and Loyola University (Chicago, IL) reported on “Preliminary findings of anti-18F-FACBC PET-CT imaging of breast cancer” [567]. Previous reporting on anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid (18F-FACBC) PET has focused mainly on prostate cancer. In this study, the goal was to characterize amino acid transport via 18F-FACBC PET/CT in benign and malignant breast lesions and correlate these results with histologic characteristics. The study included 12 women (mean age, 64 y; range, 49–89 years). The researchers noted significantly higher 18F-FACBC uptake in malignant breast tumors than in benign tumors at all imaging time points. The highest uptake was found in invasive metaplastic carcinoma when compared to other pathologic subtypes of breast cancer. Figure 13 shows examples with a high degree of 18F-FACBC uptake in a patient with disease recurrence and in a patient with newly diagnosed breast cancer. Figure 14 compares 18F-FACBC uptake in benign and malignant lesions. The authors concluded that 18F-FACBC shows promise in delineating malignant from benign breast lesions and correlates with histologic subtypes of breast cancer.

Interest in radioimmunotherapy continues to grow. Meredith et al. from the University of Alabama School of Medicine (Birmingham), ArevaMed (Bethesda, MD), and Dade Moeller Health Group (Richland, WA) reported on “Safety of first-in-human intraperitoneal α radioimmunotherapy with 212Pb-TCMC-trastuzumab” [283]. The purpose of the study was to determine the long-term safety of salvage intraperitoneal 212Pb-TCMC-trastuzumab therapy in patients with HER2-expressing malignancy. Follow-up included toxicity and other monitoring for 1 year. The
Researchers found minimal distribution of radioactivity outside the abdominal cavity, with no excess organ uptake. With escalation over 6 dose levels, minimal early agent-related toxicity was noted, with no late toxicity in the 16 patients studied. Safety data were deemed adequate for further study of this agent. The researchers noted a trend toward lower tumor markers and greater tumor regression with higher doses. Figure 15 shows anterior and posterior abdominal retention images immediately and 18 hours after injection of the $^{212}$Pb-TCMC-trastuzumab. A number of radioimmunotherapy trials are currently underway, looking at both α and β emitters.

Sörenson et al. from Uppsala University (Sweden), Affibody AB (Stockholm, Sweden), and Akademiska Hospital (Uppsala, Sweden) reported on “Accuracy of $^{68}$Ga-ABY-025 PET/CT for determination of HER2-expression in metastatic breast cancer” [156]. Their goal was to optimize peptide mass and scan timing in 10 patients with repeated scanning with this $^{68}$Ga-labeled affibody. The researchers found that a higher mass of unlabeled peptide (∼430 vs ∼80 μg) decreased uptake in liver and increased SUV in HER2-positive metastases. All HER2-positive lesions were visualized at 2 hours after injection with the high peptide dose. SUV$_{\text{max}}$ in metastases and tumors at biopsy at 2 hours were $11.6 \pm 5.2$.
in HER2-positive patients and 2.6 ± 2.2 in HER2-negative patients. At 4 hours these figures were 15.0 ± 3.4 and 2.7 ± 2.1, respectively. Test–retest reproducibility using the high peptide dose and scanning at 2 hours in 5 patients with a 1-week interval showed an intraclass correlation of SUVmax and a high repeatability coefficient. These results served to guide treatment. Anti-HER2 treatment was canceled in 1 patient and initiated in 2 patients as a result of receptor up- or downregulation. Figure 16 shows an example of 68Ga-ABY-025 PET/CT imaging in metastatic breast cancer. The effect of peptide mass and scan timing can be seen in images of liver uptake from low- and high-dose peptide. Less liver uptake is seen with the higher peptide dose, which helped to identify hepatic metastases that would not otherwise have been visualized. The comparison with 18F-FDG imaging is quite marked, another example of the maxim that when 2 tracers provide different results in the same patient, the mechanism of action of tracer accumulation is likely to be different. Immunohistochemistry also showed good correlation with 68Ga-ABY-025 PET/CT imaging, and no safety issues were noted. The authors concluded that 68Ga-ABY-025 PET/CT accurately assessed HER2 receptor status in metastatic breast cancer.

**Conclusion**

This year’s SNMMI Annual Meeting presentations continued to demonstrate the vibrant nature of our field in approaching the era of precision medicine and pathway-specific targeted therapy in oncology. Continued growth in imaging targets, theranostics, and first-in-human use of radiotracers and radiotherapeutics highlights the integral contributions we have made and will continue to make in the oncologic treatment paradigms of today and tomorrow.
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