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Highlights of Articles Published in Annals of Nuclear Medicine 2016

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Abstract

This article is the first installment of highlights of selected articles published during 2016 in the Annals of Nuclear Medicine, an official peer-reviewed journal of the Japanese Society of Nuclear Medicine. A companion article highlighting selected articles published during 2016 in the European Journal of Nuclear Medicine and Molecular Imaging, which is the official peer-reviewed journal of the European Association of Nuclear Medicine, will also appear in the Annals Nuclear Medicine. This new initiative by the respective journals will continue as an annual endeavor and is anticipated to not only enhance the scientific collaboration between Europe and Japan but also facilitate global partnership in the field of nuclear medicine and molecular imaging.

Keywords

TSPO; ^{99m}Tc -TRODAT-1; ^{123}I -BMIPP; anti- ^{18}F -FACBC; ^{68}Ga -DOTA-TRP; PET/CT; PET/MR; Radioembolization; Systematic Review; Meta-analysis; Choline

In September 2016, the editors of the European Journal of Nuclear Medicine (official journal of the European Association of Nuclear Medicine) and the Annals of Nuclear Medicine (official journal of the Japanese Society of Nuclear Medicine) announced a new section in each respective journal summarizing the highlights of published articles over the last year of the other journal (1). This new partnership is hoped to reinforce the scientific collaboration between Europe and Japan. In this first segment, I have summarized the information on 10 selected articles from an international authorship that were published in the Annals of Nuclear Medicine during January–December 2016. Although selection of articles is inherently somewhat subjective, but I attempted to provide a range of impactful topics and investigations that spanned from the preclinical to translational to clinical arenas in a concise manner.

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Compliance with Ethical Standards

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Neurology

Many central nervous system pathologies lead to microglial activation and the associated neuroinflammation (2, 3). A relevant biomarker in this process is the 18kDa translocator protein (TSPO, formerly referred to as peripheral-type benzodiazepine receptor), which is overexpressed in activated microglia (4). Toyohara and colleagues from Japan performed a preclinical and first-in-human study in one normal human volunteer of ^{11}C -CB184 (N,N-di-n-propyl-2-[2-(4- ^{11}C)-methoxyphenyl]-6,8-dichloroimidazol[1,2-a]pyridine-3-yl]-acetamide) to characterize its suitability for positron emission tomography (PET) imaging of the TSPO as the biological target (5). The authors reported an optimized synthesis method, no acute toxicity, no pharmacological effects, and specific binding to TSPO. Radioactivity in the human brain peaked at 5 minutes following intravenous administration of 807 Mbq of tracer over 1 minute. The tracer was overall homogeneously distributed in the gray matter with thalamus demonstrating slightly higher uptake and caudate nucleus and centrum semiovale showing relatively the least amount of tracer localization. The levels of radioactivity in the lungs decreased rapidly with activity levels in liver, kidney and bowel increasing gradually over 60 minutes with urinary excretion of activity. While these authors laid the groundwork, additional experience will be needed to assess the clinical utility ^{11}C -CB184 PET in the imaging evaluation of neuroinflammation and its relevance to patient care. For example, the authors note that binding affinity to TSPO may be affected by age and the rs6971 polymorphism in the TSPO gene, which was not characterized in their study (6). Additionally, the competitive advantage of ^{11}C -CB184 over other TSPO-targeted PET ligands, including those labeled with ^{18}F will need additional investigations (7).

The researchers at the Tehran University of Medical Sciences in Iran investigated the clinical utility of $^{99\text{m}}\text{Tc}$ -TRODAT-1 single photon computed tomography-computed tomography (SPECT-CT) in the differential diagnosis of movement disorders, specifically Parkinson's disease (PD), parkinsonian syndrome (PS; multiple system atrophy, progressive supranuclear palsy, cortico-basal degeneration) essential tremor (ET), dementia with Lewy bodies (DLB), drug-induced parkinsonism (DIP), etc. (8). This prospective study of 75 patients with movement disorders underwent 3h and 4h delayed SPECT-CT following intravenous administration of about 814–925 Mbq of $^{99\text{m}}\text{Tc}$ -TRODAT-1. The images were examined visually and semi-quantitatively with parameters defined as activity levels in basal ganglia in relation to amount of activities in the occipital lobe and whole brain. The biological basis for recognizing PD is the imaging evidence for loss of dopamine transporter (DAT) in the presynaptic dopaminergic nerve terminals (9). Similar to prior studies, imaging with $^{99\text{m}}\text{Tc}$ -TRODAT-1 was found to be useful as an objective recognition of PD among other disorders, which may present with similar signs and symptoms (10–12). The parameter “symptom oriented unevenness and asymmetry score”, as defined by the authors based on a combination of imaging and clinical features, provided acceptable sensitivity (80%) and specificity (83.3%) for differential diagnosis of PD/PS versus ET/DIP groups of patients; PD and PS could not be differentiated.

Cardiovascular

Dilated cardiomyopathy (DCM) is associated with significant morbidity and mortality. The disease is manifested by progressive often therapy-resistant left ventricular (LV) dysfunction (13). Cardiac resynchronization therapy (CRT) uses multisite cardiac electrical stimulation to restore LV synchrony in patients with DCM (14). CRT is often able to improve LV mechanical function, clinical symptoms, and reverse myocardial remodeling (15). However, about 30% of patients do not respond adequately to CRT intervention (14). Noninvasive imaging-based prediction of responders vs. nonresponders to CRT would be clinically useful. There have been a number of imaging investigations in this clinical space (16). Zavadovsky and colleagues from the Russian Federation studied the role of imaging information obtained from myocardial perfusion and metabolism in their combined predictive ability in assessing CRT efficacy in 63 patients with DCM and severe NYHA class III–IV heart failure (17). Both myocardial perfusion (^{99m}Tc -MIBI) and myocardial metabolism (^{123}I -BMIPP) scintigraphic studies were performed prior to CRT. Response to CRT was assessed based on change in echocardiographic parameters from before CRT to 6-month after CRT. Responders were defined as those patients with decline in LV end systolic volume of 15% from pre- to post-CRT. Based on this echocardiographic definition, there were 39 responders and 24 nonresponders. Pre-CRT scintigraphic parameters were significantly different between these 2 groups. Both myocardial perfusion and myocardial metabolism defect sizes were significantly smaller in the responders than those in nonresponders (perfusion: 7.4% vs. 11.8%; metabolism: 7.4% vs. 8.8%, respectively). Only the metabolism defect size was statistically relevant with a defect size threshold of 7.35% associated with a sensitivity of 78% and specificity of 67% in predicting CRT efficacy. This and other similar studies pave the way for building a comprehensive predictive model for tailoring CRT to those who would benefit most from this interventional procedure, which is in alignment with current emphasis on the concept of precision medicine.

Oncology

Glioblastoma is a devastating cancer with dismal prognosis even after standard of care maximal surgical resection (18). Magnetic resonance imaging (MRI) and ^{18}F -fluorodeoxyglucose (FDG) PET are not sufficiently accurate in delineating the extent of tumor prior to resection and in assessment for residual or recurrent tumor (19). The study by Kondo et al from Japan assessed the efficacy and safety of ^{18}F -fluciclovine (aka. *anti*- ^{18}F -FACBC) in a phase IIa imaging trial of 5 patients with glioma (20). The United States Food and Drug Administration (FDA) approved ^{18}F -fluciclovine (commercialized as Axumin by Blue Earth Diagnostics, Inc., Oxford, UK) on May 27, 2016, for PET imaging evaluation of men with suspected prostate cancer recurrence based on elevated prostate specific antigen (PSA) levels following prior definitive treatment (21). ^{18}F -fluciclovine is a synthetic amino acid (leucine) analog, useful for imaging increased amino acid metabolism in some tumors. Kondo et al showed that ^{18}F -fluciclovine is safe and accumulates in gliomas, which may be undetectable by contrast-enhanced T1-weighted MRI. Interestingly in this investigation, the tracer uptake reached peak activity in the brain tumor by 3 minutes and was then retained in the tumor for over 60 minutes. This is in contrast with that in prostate cancer tumors, in which the tumor tracer uptake peaks early at about 3–5 minutes post radiotracer injection

and then washes out with time. This suggests that the time-activity curves may be different across tumors, which then raises the interesting notion for interrogating the underlying biological basis and mechanism for such radiotracer uptake differences among tumors.

Gonadotropin-releasing hormone receptors (GnRH-R) is a relevant biomarker in many cancers (e.g. breast cancer, ovarian cancer, etc.)(22–24). Zoghi et al from Iran reported on the synthesis and biodistribution studies of ^{68}Ga -DOTA-triptorelin (^{68}Ga -DOTA-TRP) as a PET radioligand targeted to the GnRH-R (25). The authors reported a robust synthesis scheme with the radiotracer biodistribution demonstrating significant uptake in kidney (excretion route), stomach, and testes. In female mice bearing 4T1 breast cancer tumors, the tumor-to-blood and tumor-to-muscle ratios were 28 and >50 at 1h post intravenous tracer administration. There have been reports for radiotracers labeled with other PET radioisotopes (e.g. ^{18}F) targeted to GnRH-R (26). The report by Zoghi et al and other similar studies pave the way for development of potential therapy pairs that can provide opportunities for GnRH-R theranostics.

There have been a number of studies reported in literature comparing PET/CT and PET/MRI (27, 28). In the vast majority of these studies, PET/MRI is performed as an add-on imaging session after the clinical and/or standard of care PET/CT is performed (29–31). Ishii et al from Japan compared the diagnostic performance of PET/CT and PET/MRI in 123 patients with a variety of confirmed primary cancers (32). As typical in these types of studies, PET/CT (Biograph mCT, Siemens Healthcare, Erlangen, Germany) was performed first which was then followed by PET/MRI (Biograph mMR, Siemens Healthcare, Erlangen, Germany). The mean FDG uptake times for PET/CT and PET/MRI were 68.0 ± 8 min and 98.0 ± 14 min, respectively, with about 35 min between the start times of the two hybrid imaging sessions. The longer uptake time is anticipated to advantage the PET with PET/MRI as demonstrated with prior dual time point FDG PET studies (33). In the study by Ishii and colleagues, no statistically significant difference was observed for overall detection efficiency between the two hybrid imaging techniques, despite discrepancy for a few lesions. As anticipated, PET/CT only detected a number of lung lesions missed on PET/MRI and PET/MRI only detected few brain lesions missed on PET/CT (34). In general, given the high soft tissue contrast of MRI, those organ systems that MRI is best suited for (e.g. brain, prostate) will likely benefit from PET/MRI rather than PET/CT (35, 36). Conversely at this time, PET/CT is most appropriate for the imaging evaluation of the lung (37). No contrast agent was used for either imaging sessions, which might have also affected the final results. The authors reported total examination room time of 25 min for PET/MRI and 20 min for PET/CT. However, MRI time can be substantially longer depending upon the number and type sequences employed. Overall, it is not expected that PET/MRI will replace PET/CT due to a variety of reasons, but it is likely that at centers that have or will have PET/MRI, it will be employed for specific clinical scenarios, which will need to be defined, although use in pediatrics may lead the indications given less radiation dose with PET/MRI in comparison to PET/CT (38, 39).

Radionuclide Therapy

Selective internal radiation therapy (SIRT) has been advocated as an effective and safe treatment of unresectable primary and metastatic hepatic lesions (40, 41). The procedure involves pretreatment planning for vascular mapping, possible embolization of selected vessels to prevent subsequent radioembolization of nontarget tissue, ^{99m}Tc -MAA hepatic perfusion imaging with pulmonary and gastrointestinal tract shunt determination, and if appropriate, intraarterial hepatic injection of the radioactive resin (^{90}Y -SIR-Spheres) or glass (^{90}Y -TheraSphere), and post-treatment Bremsstrahlung imaging to confirm hepatic localization of the radioactive spheres (42). Soydal et al from Turkey reported on a retrospective investigation to assess the prognostic factors that predict overall survival in 16 patients with chemo-refractory cholangiocarcinoma who underwent radioembolization (43). FDG PET/CT was performed before and 3 months after treatment. At the third month 30% of patient were responsive to treatment based on RECIST criteria. About 80% of patients had FDG-avid hepatic lesions (defined as activity above background liver activity). The mean follow-up period was 243 days (range 98–839 days) during which 12 of 16 patients died. The authors concluded, through a multivariate Cox regression analysis, that FDG avidity and the dimension of the largest liver lesion, tumor load, and radiological response were significant prognostic factors in this clinical setting. Patients with non-FDG avid tumors, lower overall hepatic tumor load, and smaller tumors fared better with longer overall survival after radioembolization therapy. This study showed that number, size and metabolic activity of hepatic tumors (readily obtained with FDG PET/CT) could predict overall survival in these patients.

Systematic Reviews and Meta-Analyses

Systematic reviews and meta-analysis are important contributions to the relevant literature (44). This section highlights 2 such investigations that appeared in the Annals of Nuclear Medicine in 2016. Li et al from China performed a systematic review and meta-analysis of FDG PET and PET/CT in in detection of recurrent gastric cancer after surgical resection (45). Gastric adenocarcinoma recurs in more than half of patients even after complete primary tumor resection with curative intent (46, 47). The standard of care methods such as contrast-enhanced CT imaging, endoscopy and tumor markers are limited in detection, localization and characterization of disease. This study included 14 published investigations from 2002–2015 involving a total of 828 patients. On a per patient basis, the pooled sensitivity and pooled specificity were 85% [95% confidence interval (CI): 75%–92%] and 78% [95% CI: 72%–84%], respectively. On a per lesion basis, the pooled sensitivity was 75% (95% CI: 61%–86%). Per lesion basis pooled specificity could not be determined since there was no information on sites without recurrence and no FDG uptake. There were a number of sources for heterogeneity among studies including exclusion of signet cell and mucinous carcinomas (probably because of generally low FDG avidity), variety in reference standard for PET findings, and differences in incidence rates of cancer given that the majority of the articles were from Asia with only 2 studies from the western countries. The results of this systematic review and meta-analysis, supporting the efficacy of FDG PET in this clinical setting, were overall similar to a prior report from the same institution in

Shanghai, China, that involved 9 studies (526 patients) with a pooled sensitivity of 78% (95% CI: 68%–86%), and a pooled specificity of 82% (95% CI: 76%–87%) (48).

Another interesting systematic review and meta-analysis by von Eyben and Kairemo assessed whether there is a significant difference between lesion detection rates of ^{11}C -choline and ^{18}F -fluorocholine (FCH) in PET/CT imaging evaluation of men with biochemical recurrence of prostate cancer after primary treatment with radical prostatectomy or external radiation therapy (49). About 30% of men develop recurrent disease after primary treatment with curative intent. While some of these cases may be sourced from insufficient initial staging with the current methods, some cases may relate to early escape of malignant cells or evolution of cancer deposits cells into expressing a more aggressive biology. Biochemical recurrence of prostate cancer is defined as a rise in serum prostate-specific membrane antigen (PSA) level from unmeasurable to levels >0.2 ng/mL after radical prostatectomy with 2 subsequent confirmatory stable or rising PSA measurements (50). In the clinical setting of prior external radiation therapy for primary tumor, biochemical recurrence is defined as rise in PSA to levels >2.0 ng/mL above the nadir PSA level achieved after primary radiation therapy (51). It must be recognized that “pure” biochemical failure is the state of defined elevated PSA without standard of care imaging (contrast-enhanced chest, abdomen, and pelvis CT, bone scintigraphy, and most often now multiparametric magnetic resonance imaging of prostate bed) evidence of locally recurrent or metastatic disease. Radiolabeled choline PET has received tremendous attention over the past many years in providing an alternative effective imaging method for detecting and localizing disease in men with biochemical recurrence of prostate cancer (52–57). In the systematic review and meta-analysis reported in *Annals of Nuclear Medicine*, von Eyben and Kairemo evaluated the technical and clinical aspects of 18 articles (6 ^{11}C -choline, 12 FCH) comprising 2213 patients with suspected biochemical failure of prostate cancer with a mean PSA level of 3.6 ± 2.7 ng/mL (range 0.5–10.5 ng/mL). Although there was statistically significant difference in the mean administered activity (^{11}C -choline: 561 ± 122 Mbq, FCH: 293 ± 47 Mbq) and uptake time (^{11}C -choline: 5 min, FCH: 29 ± 24 min), there was nevertheless no statistically significant difference between the lesion detection rates (^{11}C -choline: $30 \pm 5\%$, FCH: 39 ± 5 , $p=0.26$). The authors concluded that in the clinically relevant PSA levels of 1–10 ng/mL, there was no statistically significant difference in the diagnostic performance between ^{11}C -choline and FCH. A prior study had also shown that there was excellent concordance between radiolabeled choline and radiolabeled acetate, on both a per-lesion and a per-patient basis, in this clinical setting (58). The combined results of these studies suggest that regardless of which lipogenesis PET radiotracer is employed, their diagnostic performance is essentially similar in the imaging evaluation of men with biochemical recurrence of prostate cancer.

National Survey

Watanabe and colleagues reported on a national survey of the actual administered radioactivity to adults for a variety of single-photon radiotracers as well as for FDG (59). The nationwide survey was conducted for nearly 2 months from November 25, 2014 to January 16, 2015 and was sent to 1249 nuclear medicine facilities in Japan. The survey questionnaire included items including average administered adult dose for common nuclear

medicine procedures, number of scanners, number of staff members, and number of technologists and physicians. The primary objective of this survey was to determine the Japanese diagnostic reference levels (DLRs) for administered activities in adults and to decipher whether those levels are similar to those in the other regions of the world including Europe and North America. The survey response rate was a respectable 41%. The authors established through the results of this nationwide survey that the DLRs in Japan are in line with those in Europe except for ^{201}Tl -Cl myocardial perfusion scintigraphy (Japan: 180 MBq, Europe: 75–150 MBq), and for $^{99\text{m}}\text{Tc}$ -pertechnetate thyroid scintigraphy (Japan: 300 MBq, Europe: 75–222 MBq). Conversely for FDG in oncologic PET scintigraphy and ^{123}I -NaI thyroid scintigraphy, the Japanese DRLs were at the lowest level of European DRLs. Moreover, none of the Japanese DRLs exceeded the upper limits of those recommended by the Society of Nuclear Medicine and Molecular Imaging (SNMMI). The authors concluded that their survey not only helped in the development of Japanese DRLs for nuclear medicine but also it demonstrated that the Japanese nuclear medicine facilities strongly follow the guidelines that are within the range of administered activities in Europe and North America.

Conclusion

The selected 10 articles published in the Annals of Nuclear Medicine during 2016 provided an interesting and impactful range of information in nuclear medicine and molecular imaging. The initiative of the EJNMMI and Annals of Nuclear Medicine editors of providing review of selected articles published during the past year in respective journals will be informative to the readership of either journal and enhance global scientific partnership.

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