FROM THE LITERATURE

Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.

68Ga-DOTATATE in Preoperative PC/PGL

Gild et al. from Royal North Short Hospital and the University of Sydney (both in Sydney, Australia) reported on May 9 ahead of print in *Clinical Endocrinology* on a study describing the utility of ^{68}Ga-DOTATATE somatostatin receptor imaging agents in primary, preoperative assessment of paragangliomas and pheochromocytomas. The retrospective analysis included 73 patients (46 with suspected pheochromocytomas and 27 with suspected paragangliomas), of whom 36 were imaged with ^{68}Ga-DOTATATE PET/CT during primary assessment and 37 in postoperative follow-up. As a comparison group, the study also included scans from 30 patients without disease (20 with normal adrenals and 10 with incidental adenomas). The researchers found that PET/CT had an 88% sensitivity for pheochromocytomas and 100% for paragangliomas, with false-negatives in 2 of 10 pheochromocytomas <28 mm in size and in 1 of 14 pheochromocytomas >28 mm with features of cystic degeneration. The SUV_{max} for both paragangliomas and pheochromocytomas was more than twice that of adrenal adeno-

mas. The authors recommended that somatostatin receptor imaging "should be performed as part of primary assessment in all suspected paragangliomas (due to higher risk of multifocal lesions) and in pheochromocytomas suspected to be associated with hereditary syndromes or metastases."

Clinical Endocrinology

18F-FDG PET and Prediction of AD Conversion

In an article e-published on May 14 ahead of print in *Molecular Diagnosis & Therapy,* Kang et al. from Gachon University College of Medicine (Incheon), Seoul National University and College of Medicine, Inje University College of Medicine, and the National Evidence-Based Healthcare Collaborating Agency (Seoul; all in the Republic of Korea) reported on a study assessing the value of ^{18}F-FDG PET in predicting conversion to Alzheimer disease (AD) in patients with mild cognitive impairment (MCI), including comparison of visual reading and computer-assisted analyses. The study included a total of 54 patients with MCI who underwent ^{18}F-FDG PET imaging at baseline and 2 y later at final diagnostic evaluation. The resulting images were analyzed by traditional visual rating, a composite score of visual rating of the brain cortices, and a composite score generated by computer-assisted analysis. Receiver operating characteristic (ROC) curves were compared in the 3 methods to assess predictive values. At 2 y, 19 patients (35.2%) had converted from MCI to AD. Areas under the curve of the ROC curve were compared among the 3 image assessment approaches: traditional visual rating, 0.67; composite score of visual rating, 0.76; and computer-assisted analysis, 0.79. The ROC curves of the composite scores of the visual rating and computer-assisted analysis were comparable and were similar in predicting AD conversion. The authors concluded that "FDG PET may be a useful tool

for screening AD conversion in patients with MCI, when using composite score, regardless of the method of interpretation."

Molecular Diagnosis & Therapy

177Lu-PSMA-617 in Metastatic Prostate Cancer

Hofman et al. from the Peter MacCallum Cancer Centre/University of Melbourne (Australia) reported on May 7 ahead of print in *The Lancet. Oncology* on a single-center, single-arm phase II study investigating the safety, efficacy, and effect on quality of life of ^{177}Lu–prostate-specific membrane antigen–617 (^{177}Lu-PSMA-617) therapy in men with metastatic castration-resistant prostate cancer who had progressed after standard treatments. The study included 30 men, of whom 26 (87%) had received at least 1 line of previous chemotherapy (80% docetaxel and 47% cabazitaxel) and 25 (83%) had received prior abiraterone acetate, enzalutamide, or both. Patients underwent a screening PSMA and/or ^{18}F-FDG PET/CT to confirm high PSMA expression. Progressive disease was defined by imaging or new pain in an area of radiographically evident disease. Patients were required to have an Eastern Cooperative Oncology Group performance status score of ≤2 and received up to 4 cycles of intravenous ^{177}Lu-PSMA-617 at 6 weekly intervals, with a mean of 7.5 GBq per cycle. Prostate-specific antigen (PSA) response was defined as a $>50\%$ decline from baseline, with toxicity reported using the Common Terminology Criteria for Adverse Events. Imaging responses (on bone scan, CT, PSMA, and ^{18}F-FDG PET/CT) and quality of life were also assessed up to 3 mo after completion of treatment. The researchers found that 17 (57%) of the 30 patients achieved a PSA decline of $\geq50\%$ with no treatment-related deaths. Toxic effects related to treatment were grade 1 dry mouth (26 patients), grades 1 and 2 transient nausea (15), and grades 1

and 2 fatigue (15). Grades 3 or 4 thrombocytopenia possibly attributed to ^{177}Lu-PSMA-617 were seen in 4 patients. In addition, objective response in nodal or visceral disease was seen in 14 (82%) of 17 patients with measurable disease. Eleven (37%) patients experienced a $\geq$10-point improvement in global health score by the second cycle of treatment, with clinically meaningful improvements in pain severity and interference scores recorded at all time points. The authors concluded that because of the high response rates, low toxic effects, and reduction of pain with ^{177}Lu-PSMA-617 in men with metastatic castration-resistant prostate cancer who have progressed after conventional treatments, randomized controlled trials should be pursued to further assess efficacy in comparison with current standards of care.

The Lancet. Oncology

^{18}F-FDG PET/CT and Thyroid Incidentalomas

In an article e-published on May 15 ahead of print in *Thyroid*, Chung et al. from the Asan Medical Center at the University of Ulsan College of Medicine (Seoul) and the Namwon Medical Center (both in the Republic of Korea) reported on a study using ultrasound to stratify the risk of malignancy in thyroid incidentalomas detected on ^{18}F-FDG PET/CT. The study included PET/CT imaging from 877 patients with 907 thyroid nodules who also had undergone ultrasound evaluation to assess focal thyroid uptake. The ultrasound images were retrospectively reviewed according to American Thyroid Association (ATA) and Korean Thyroid Image Reporting and Data System (K-TIRADS) guidelines, and calculated malignancy risks were compared with estimated risks as suggested by the guidelines. The overall malignancy risk of thyroid incidentalomas detected on ^{18}F-FDG PET/CT in patients in the study was 54.7%. The malignancy risks of thyroid incidentalomas with high and intermediate suspicion (93.5% and 52.1%, respectively) in the study were higher than those stratified using ATA criteria. The

malignancy risks of thyroid incidentalomas with low and very low suspicion (10.1% and 0%, respectively) were within the guideline ranges. Results were similar when incidentalomas were stratified according to the K-TIRADS criteria. The authors concluded that "ultrasound examinations can be used to stratify the malignancy risk of thyroid incidentalomas detected on ^{18}F-FDG PET/CT" and that, because the risk of malignancy did not increase in thyroid incidentalomas with low and very low suspicion, only selective biopsies may be needed in these categories.

Thyroid

[89]Zr-Girentuximab PET/CT in Clear Cell Renal Cell Carcinoma

Hekman et al. from the Radboud Medical Center (Nijmegen, The Netherlands) and the Royal Marsden Hospital (London, UK) e-published on May 3 ahead of print in *European Urology* an article exploring the value of [89]Zr-labeled girentuximab PET/CT imaging in diagnostic challenges associated with clear cell renal cell carcinoma (CCRCC). [89]Zr-girentuximab is an anti–carbonic anhydrase IX (CAIX) monoclonal antibody with promise in CCRCC, in which 95% of lesions highly express CAIX. The study included 30 patients (16 with a primary renal mass and 14 with a history of CCRCC). Each participant underwent [89]Zr-girentuximab PET/CT 4 or 5 days after injection. Imaging results guided decision making (assignment to surgery or active surveillance) when renal masses were indistinct. All resected PET-positive primary lesions were found to be CCRCCs, with no progression found in PET-negative masses. [89]Zr-girentuximab PET/CT was useful in patients with suspected recurrent/metastatic disease in confirming or excluding CCRCC, evaluating disease extent, and differentiating CCRCCs from other cancers. [89]Zr-girentuximab PET/CT in suspected recurrent/metastatic disease resulted in a major change in clinical management in 5 patients, and repeat biopsy was deemed avoidable in 3 patients. The authors concluded

that "[89]Zr-girentuximab PET/CT is a valuable diagnostic tool that can guide clinical decision making in case of diagnostic dilemmas concerning CCRCC suspicion."

European Urology

^{18}F-FDG PET and Liver Transplant Rejection

In an article e-published on May 15 ahead of print in *Surgery*, Watson et al. from the University of Louisville (KY) reported on a study evaluating the effectiveness of ^{18}F-FDG PET in detecting the activation and increased metabolic activity of T cells associated with acute cellular rejection in liver transplantation. The study included 88 patients who underwent PET imaging at 7 and 17 d after orthotopic liver transplantation. In some patients with a suspicion of rejection, a third PET study was acquired, with a fourth at resolution of rejection. Eighteen patients (20.5%) were found to have histologically proven acute cellular rejection over a 16 $\pm$ 11–d follow-up. Although no significant differences in SUVs were noted between nonrejecters and rejecters at d-7 imaging, SUVs at the third PET/CT in the rejection cohort were significantly higher than their d-7 results. The authors concluded that "increased signal on ^{18}F-FDG PET over baseline is associated with acute cellular rejection in liver transplant recipients" and that "additional prospective validation studies are essential to define the role of ^{18}F-FDG PET scan as an early marker for acute cellular rejection."

Surgery

Dedicated Breast PET and Cancer Grade

Masumoto et al. from Hiroshima University/Hiroshima University Hospital (Japan) reported on May 19 ahead of print in *Breast Cancer Research and Treatment* on a study looking at correlations between ^{18}F-FDG uptake on dedicated breast PET and clinical and pathologic features in breast cancer, with a special focus on intratumoral heterogeneous distribution of ^{18}F-FDG. The study included 195 women

with invasive breast cancer who underwent preoperative whole-body PET and dedicated breast PET imaging. SUV_{max} results with the 2 PET studies were compared with clinical stage, nuclear grade, Ki67 proliferation index, and estrogen receptor (ER) and human epidermal growth factor receptor type 2 (HER2) statuses, along with intratumoral heterogeneity of ^{18}F-FDG distribution on dedicated breast PET. The SUV_{max} of dedicated breast PET was found to be significantly correlated with the clinical T stage, N stage, nuclear grade, and Ki67 proliferation index, in addition to ER and HER2 statuses. Intratumoral heterogeneous tracer distribution on dedicated breast PET was significantly correlated with high nuclear grade and high Ki67 proliferation index. The authors concluded that although SUV_{max} results with both dedicated breast PET and whole-body PET correlate with clinicopathologic factors, "intratumoral heterogeneity on dedicated breast PET provides predictive value for malignancy grade and could inform therapeutic decisions."

Breast Cancer Research and Treatment

PET and PET/CT in RT Planning for Anal Cancer

In an article in the June issue of *Critical Reviews in Oncology/Hematology* (2018;126:6–12), Albertsson et al. from Sahlgrenska University Hospital (Gothenburg) and the University of Gothenburg (both in Sweden) reported on a systematic review and metaanalysis of the use of PET/CT in improving the accuracy of radiation therapy planning in patients with anal cancer. The review included assessment of impact on survival, quality of life, symptom score, and changes in target definition and treatment intention. After a systematic search of major literature databases, 10 cross-sectional studies met the inclusion criteria (although no data were available on survival or quality of life). PET/CT was found in summary estimates to change target definition in 23% of patients and to change treat-

ment intent from curative to palliative in 3%. The authors concluded by noting that "almost 1 in 4 patients had a change in target definition, which supports the use of PET/CT in radiation therapy planning, but the consequence regarding survival and quality of life is still uncertain."

Critical Reviews in Oncology/Hematology

^{11}C-PBR28 PET and Integrated MR Imaging in ALS

Alshikho et al. from the Massachusetts General Hospital/Harvard Medical School (Boston, MA) reported in an article e-published on May 8 ahead of print in *Annals of Neurology*, on a study characterizing longitudinal changes and gray/white matter distribution of ^{11}C-PBR28 brain uptake on PET and MR imaging in patients with amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS). The study included 53 patients with ALS, 11 with PLS, and 21 healthy controls who underwent integrated ^{11}C-PBR28 PET–MR brain imaging. Patients were evaluated clinically using the Upper Motor Neuron Burden (UMNB) score and the revised ALS Functional Rating Score (ALSFRS-R). The SUV ratio (SUVR) was compared between groups, and cortical thickness and fractional anisotropy were correlated with SUVRs and clinical data. In 10 participants, ^{11}C-PBR28 uptake and ALSFRS-R assessments were compared over 6 mo. Whole brain voxel-wise, surface-based, and region-of-interest analyses showed increased ^{11}C-PBR28 uptake on PET in the precentral and paracentral gyri in ALS and in the subcortical white matter for the same regions in PLS. These increases in uptake correlated with cortical thinning, reduced fractional anisotropy, and increased mean diffusivity on MR imaging and clinically with higher UMNB scores. Significant changes were not detected in ^{11}C-PBR28 uptake over the 6-mo follow-up period, despite clinical progression.

Annals of Neurology

Delayed PET/CT in Newly Diagnosed Breast Cancer

In an article in the May 9 issue of *BMC Medical Imaging* (2018;18 [1]:11), Baun et al. from Odense University Hospital (Denmark) and the University of Pennsylvania (Philadelphia) analyzed changes in SUV between 1- and 3-h time-point ^{18}F-FDG PET/CT imaging in local and distant lesions in patients with recurrent breast cancer. The authors also investigated the effect of partial-volume correction in different types of metastases using semiautomatic quantitative software. The study included 102 women with suspected breast cancer recurrence who underwent whole-body ^{18}F-FDG PET/CT at 1 and 3 h after injection. SUV_{max}, SUV_{mean}, and partial volume–corrected SUV_{mean} were assessed semiquantitatively in malignant lesions, with reference values in healthy liver tissue. Forty-one patients were found to have recurrent disease at biopsy, with a median of 15 lesions (range, 1–70) for a total of 337 malignant lesions. The SUV_{max} of malignant lesions increased from 6.4 ± 3.4 at 1 h to 8.1 ± 4.4 at 1 to 3 h (in breast by 25%, lung, 40%, lymph nodes, 33%, and bone lesions, 27%), with similar patterns in SUV_{mean} without partial-volume correction. Application of partial-volume correction increased the average SUV_{mean} significantly, from 63% to 71% at the 2 time points. This change was most marked in breast lesions at 3 h, where partial volume–corrected SUV_{mean} increased by 87% compared to uncorrected SUV_{mean}. The authors concluded that although SUVs increased from 1 to 3 h in malignant lesions, SUVs of distant recurrence averaged about 2 times as high as those of local recurrence, and partial volume corrections significantly increased these values, "it is questionable if these relatively modest quantitative advances of 3h imaging are sufficient to warrant delayed imaging in this patient group."

BMC Medical Imaging

PET/CT, Inflammation, and Carotid Disease

Chowdhury et al. from Addenbrooke's Hospital/University of Cambridge (UK) reported on May 2 ahead of print in the *European Journal of Vascular and Endovascular Surgery* on a metaanalysis of studies on ^{18}F-FDG uptake in PET/CT in patients with symptomatic and asymptomatic carotid artery disease. The systematic review began with a search of 17 y of citations in the MEDLINE database with keywords "inflammation", "FDG," and "stroke" and a focus on the degree of arterial vascular inflammation determined by ^{18}F-FDG uptake on PET. Fourteen studies including 539 patients met the criteria for the metaanalysis. A comparison of ^{18}F-FDG uptake in carotid arteries in symptomatic and asymptomatic disease produced a standard mean difference of 0.94. The authors concluded that "PET/CT using ^{18}F-FDG can demonstrate carotid plaque inflammation, and is a marker of symptomatic disease," and added that additional studies are needed to more clearly define the clinical utility of PET/CT as a risk prediction tool in this setting.

European Journal of Vascular and Endovascular Surgery

PETAL Phase III Report

In an article e-published on May 11 ahead of print in the *Journal of Clinical Oncology*, Dührsen et al. from a consortium of 21 sites in Germany and 1 in The Netherlands reported on results from the PET-Guided Therapy of Aggressive Non-Hodgkin Lymphomas (PETAL) multicenter, randomized phase III trial. The authors reviewed the data to determine whether PET imaging can guide therapy in patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. The study included 862 newly diagnosed patients who received 2 cycles of CHOP plus rituximab (R-CHOP) in CD20-positive lymphomas, with a post-CHOP PET scan that evaluated changes in SUV_{max} over baseline values. Patients with positive PET imaging ($n = 108$ [12.5%]) were randomized to 6 additional R-CHOP cycles ($n = 52$) or to 6 blocks of an intensive Burkitt lymphoma chemotherapeutic protocol ($n = 56$). One group of patients ($n = 255$) with CD20-positive lymphomas who were negative on PET were randomly assigned to receive 4 additional cycles of R-CHOP ($n = 129$) or R-CHOP plus 2 additional doses of rituximab ($n = 126$). Two-year event-free survival rates in PET-positive patients were 42% in those assigned to R-CHOP and 31.6% in those assigned to the Burkitt protocol. Those assigned to the Burkitt protocol experienced significantly more toxicities. Two-year event-free survival rates in PET-positive patients were 76.4% in those with additional R-CHOP cycles and 73.5% in those with both additional R-CHOP and rituximab. The authors concluded that interim PET after initial R-CHOP predicted survival in patients with aggressive lymphomas but added that "PET-based treatment intensification did not improve outcome."

Journal of Clinical Oncology

PET, Tau Burden, and Physical Activity

In an article e-published on May 11 ahead of print in the *Journal of Alzheimer's Disease*, Brown et al. from Murdoch University, Hollywood Private Hospital (Nedlands), Edith Cowan University (Joondalup), CSIRO Health and Biosecurity (Herston), Curtin University, the University of Melbourne, the National Ageing Research Institute (Parkville), Austin Health (Heidelberg), and Macquarie University (Sydney; all in Australia) reported on a retrospective study of PET-quantified tau burden and self-reported physical activity in cognitively healthy older adults. The researchers used data from the Australian Imaging, Biomarkers, and Lifestyle study to create a group of 43 adults self-described as maintaining low-to-moderate physical activity ($n = 16$) or high physical activity ($n = 27$). All participants underwent ^{18}F-AV1451 PET imaging. A significantly higher neocortical tau burden was identified in the low-to-moderate physical activity group compared with that seen in the high physical activity group, a difference that was evident locally in the temporoparietal cortex and prefrontal cortex. Because these results suggest an association between self-reported physical activity and brain tau burden, the authors concluded that "future longitudinal and interventional studies utilizing larger samples sizes are vital to further investigate the nature of the relationship between tau and physical activity."

Journal of Alzheimer's Disease

PET/CT in RT Planning for Esophageal Cancer

Jimenez-Jimenez et al. from St. Lucia University General Hospital (Cartagena), the Clínica IMQ Zorrotzaurre (Bilbao), Hospital Universitari Son Espases (Palma de Mallorca), and the Complejo Hospitalario Universitario de Albacete (all in Spain) reported on May 2 ahead of print in *Clinical & Translational Oncology* on a comparison of metrics (volumes and tumor lengths) using ^{18}F-FDG PT/CT or CT simulation in the segmentation process for radiotherapy planning in esophageal cancer. The study included data from 29 patients with esophageal cancer who underwent a single PET/CT simulation scan. Using the scans, 2 separate gross tumor volumes were defined: 1 based on CT data alone and another based on fused PET/CT data. Gross tumor volume and maximum tumor diameter measurements were larger with PET/CT, but the length of primary tumors was greater on CT; however, these differences were not statistically significant. Gross node volume was significantly larger for PET/CT. Dice similarity coefficient analysis indicated excellent agreement for gross tumor volume but was quite low for gross node volume. The authors concluded that "CT simulation, without taking into account PET/CT information, might leave cancer-involved nodes out of the radiotherapy-delineated volumes."

Clinical & Translational Oncology

PET/CT in Pediatric Pancreatic Cancers

In an article e-published on May 11 ahead of print in *Pediatric Blood & Cancer*, Bohl et al. from Methodist University Hospital, St. Jude Children's Research Hospital, and the University of Tennessee Health Science Center (all in Memphis, TN) characterized the metabolism of primary and secondary tumors of the pancreas in pediatric patients. Both primary pancreatic carcinoma and pancreatic metastases are rare in the pediatric population. The study included a broad retrospective analysis of pediatric patients who had undergone ^{18}F-FDG PET/CT imaging for such disease. Three patients were identified with primary pancreatic cancer (1 with pancreatoblastoma, 1 with solid pseudopapillary tumor, and 1 with adenocarcinoma). All tumors were found to show elevated ^{18}F-FDG uptake on PET/CT. A larger group of 12 patients with metastatic disease was identified (5 with non-Hodgkin lymphoma, 3 with osteosarcomas, 2 with rhabdomyosarcomas, 1 with a Ewing sarcoma family tumor, and 1 with a malignant rhabdoid tumor). Tracer uptake was elevated in each of the tumors of patients with metastatic disease within the pancreas. The authors concluded that "both primary malignancies and metastatic disease within the pancreas, though very rare in children, adolescents, and young adults, are metabolically active and can be functionally characterized using FDG-PET CT."

Pediatric Blood & Cancer

BAT and Sympathetic Activity in Narcolepsy

Enevoldsen et al. from the Rigshospitalet and the University of Copenhagen (both in Copenhagen, Denmark) reported on May 15 ahead of print in *Sleep* on a study investigating the activity of brown adipose tissue (BAT) in patients with type 1 narcolepsy during cold exposure. ^{123}I-MIBG SPECT and ^{18}F-FDG PET were used to visualize BAT sympathetic innervation and metabolic activity, respectively. The authors focused on the question of whether orexin deficiency contributes to altered nonshivering thermoregulation in narcolepsy. The study included 7 patients with type-1 narcolepsy and 7 healthy controls who underwent imaging with both modalities after 2 h of cold exposure. Levels of 8 hormones associated with BAT activity regulation were also measured before and after cold exposure. Although both ^{123}I-MIBG and ^{18}F-FDG uptake was evident in all participants after cold exposure, BAT activity did not differ significantly between healthy controls and those with narcolepsy. Levels of glucagon-like peptide–1 (GLP-1) were higher in individuals with type 1 narcolepsy than in controls, but the levels were not altered by cold exposure in either group. Fibroblast growth factor–1 concentration was found to be lower after cold exposure in both groups of participants. The authors noted that imaging allowed visual identification of both BAT sympathetic and metabolic activities after cold exposure in patients with type 1 narcolepsy. They added that "increased GLP-1 in narcolepsy may suggest autonomic dysfunction with metabolic changes" and that "BAT is functional after cold exposure in spite of the loss of orexinergic neurons in narcolepsy."

Sleep

Reviews

Review articles provide an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent literature. The Newsline editor recommends several systematic and general reviews accessioned into the PubMed database in May and June. Bayan et al. from Columbia University College of Physicians and Surgeons/Columbia University Medical Center (New York, NY) and the University of Arizona/University of Arizona Cancer Center at Dignity Health (Phoenix, AZ) published "A review of noninvasive imaging in extramammary Paget's disease" on May 15 ahead of print in the *Journal of the European Academy of Dermatology and Venereology*. In an article published on May 11 online in *Radiation Oncology* (2018;13[1]:90), Zschaeck and colleagues from the Charité Universitätsmedizin Berlin (Germany) and a large consortium of German, Swiss, and Austrian cancer research groups authored "PSMA-PET based radiotherapy: A review of initial experiences, survey on current practice and future perspective." Yousaf et al. from the Institute of Psychiatry, Psychology, and Neuroscience at King's College London (UK) described the role of radiolabeled agents and associated modalities in "Neuroimaging in Lewy body dementia" on May 14 ahead of print in the *Journal of Neurology*. In "Alzheimer's disease neuroimaging," e-published on May 11 ahead of print in *Current Opinion in Neurology*, Whitwell, from the Mayo Clinic (Rochester, MN), discussed the contribution of neuroimaging studies to the understanding of Alzheimer disease. Zhang and Guan, from the Shanxi Cancer Hospital and Institute (Taiyuan, China) surveyed "PET/CT in the diagnosis and prognosis of osteosarcoma" on June 1 in *Frontiers in Bioscience (Landmark Edition)* (2018;23:2157–2165).