

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.

PSMA PET/CT Risk-Stratification Tool

Xiang, from the University of California at Los Angeles, and a multiinstitutional cohort of investigators reported in the December 1 issue of *JAMA Network Open* (2021;4[12]:e2138550) on the prognostic significance of a nomogram developed to model an individual's risk of nonlocalized upstaging of high-risk prostate cancer on prostate-specific membrane antigen (PSMA)-based PET/CT. The researchers also compared the nomogram's performance with that of existing risk-stratification tools. The 15-center, multinational study included 5,275 patients diagnosed with high- or very high-risk prostate cancer (prostate-specific antigen [PSA] >20 ng/mL, Gleason score of 8–10, and/or clinical stage of T3–T4, with no evidence of nodal or metastatic disease on conventional workup). Data calculated in the nomogram for PSMA upstaging included the biopsy Gleason score, percentage positive systematic biopsy cores, clinical T category, and PSA levels. Over a median follow-up of 5.1 y, 1,895 (36%) participants had biochemical recurrence, 851 (16%) developed distant metastases, and 242 (5%) died of

prostate cancer. The PSMA upstage probability was significantly prognostic for all clinical endpoints, with 8-y concordance indices of 0.63 for biochemical recurrence, 0.69 for distant metastases, 0.71 for prostate cancer-specific mortality, and 0.60 for overall survival. The PSMA nomogram outperformed existing risk-stratification tools, except for performance similar to that of the Staging Collaboration for Cancer of the Prostate for prostate cancer-specific mortality. Results were validated against secondary cohorts from a national database. The authors concluded that these findings suggest that PSMA upstage probability is associated with long-term, clinically meaningful endpoints, with superior risk discrimination compared with existing tools. They added that “formerly occult, PSMA PET/CT-detectable nonlocalized disease may be the main driver of outcomes in high-risk patients.”

JAMA Network Open

SPECT/CT in Complex Foot and Ankle Diagnosis

In an article published on December 7 ahead of print in *Foot & Ankle Specialist*, Ghani et al. from the Royal National Orthopaedic Hospital (Stanmore, UK) reported on an assessment of the value of SPECT/CT in patients with complex but nonarthritic and nonneoplastic foot and ankle pathology with unclear diagnoses after conventional imaging. The retrospective research, which began with a dataset of 297 SPECT/CT foot and ankle studies, found only 18 (age range, 16–56 y) performed for nonarthritic/nonneoplastic diagnoses. The resulting SPECT/CT findings differed from provisional diagnoses in 10 (56%) of the 18 patients, leading to changes in treatment planning and significant improvements in 8 of these 10 patients. In the remaining 8 patients, SPECT/CT was useful in confirming provisional diagnoses, which had been uncertain on conventional imaging. A total of 15 of the 18 patients (83%) showed improvements in symptoms after

management affected by SPECT/CT diagnoses. The authors concluded that these results highlight “the added value of SPECT/CT in patients presenting with nonarthritic and nonneoplastic foot and ankle conditions in which there is diagnostic uncertainty after conventional imaging” and noted that in their practice they have found SPECT/CT to be a useful investigative modality in assessing these cases.

Foot & Ankle Specialist

Dual-Tracer PET/CT in Renal Cell Carcinoma

Tariq et al. from the Royal Brisbane and Women's Hospital (Brisbane), the University of Queensland (Brisbane), Redcliffe Hospital, Wesley Urology Clinic/The Wesley Hospital (Brisbane), and the Princess Alexandra Hospital (Brisbane; all in Australia) reported on December 8 online ahead of print in *Urologic Oncology* on dual-tracer ^{18}F -FDG and prostate-specific membrane antigen (PSMA)-based PET/CT compared with standard-of-care imaging for the characterization, staging, and restaging of renal cell carcinoma. The retrospective, multicenter study included 11 patients (mean age, 65.5 y; 7 men, 4 women) who underwent dual-tracer PET/CT after conventional imaging. Indications for referral to dual-tracer PET were staging (36%) and restaging after radical/partial nephrectomy (64%). Mixed patterns of uptake in primary tumor assessment were concordant in 40% and discordant in 60% (20% favoring PSMA and 40% favoring ^{18}F -FDG). Tracer uptake in metastatic disease was concordant in 6 patients (55%), in agreement as negative in 3 (27%), and discordant in 2 (favoring PSMA). PET was superior to standard-of-care imaging for assessment of metastatic disease in 5 patients (45%) and equivalent for the remainder, with resulting management changes in 3 (27%). The authors noted that PSMA tracers and ^{18}F -FDG offer complimentary advantages in PET/CT assessment of primary and metastatic

renal cell carcinoma and that the intensity of avidity of the tracers may assist in prognostication.

Urologic Oncology

US-Based Respiratory Motion Detection in PET/CT

In an article published on December 10 ahead of print in *Physics in Medicine and Biology*, Madore et al. from the Harvard Medical School/Brigham and Women's Hospital (Boston, MA), the University of Oxford (UK), National Sun Yat-Sen University (Kaohsiung, Taiwan), Amazon Robotics (Westborough, MA), Eindhoven University of Technology (The Netherlands), and the University of Pennsylvania Perelman School of Medicine (Philadelphia) reported on development and testing of small ultrasound-based sensors, referred to as organ-configuration motion (OCM) sensors, that attach to the skin and provide motion-sensitive information to allow respiratory gating during PET imaging. In the study, both a motion phantom with an ^{18}F -FDG solution and imaging in 2 cancer patients were used to test the sensors. In the phantom and in patients, the OCM signals were used to help reconstruct data into time series of motion-resolved images accurately capturing underlying motion. In 1 patient, a single large lesion was seen to be mostly stationary through the breathing cycle. In the second patient, several small lesions were mobile during breathing, and the sensors captured breathing-related displacements. The authors noted that this relatively inexpensive and simple hardware solution, which attaches to the skin rather than walls or ceilings, is advantageous because it can accompany patients from 1 procedure to another, with the potential for gathering more consistent and useful data on breathing motion-related changes.

Physics in Medicine and Biology

Brain Metabolism Patterns and Epilepsy Death Risk

Whatley, from the University College of London/Queen Square Institute of Neurology (UK), and a consortium of researchers from the UK, Canada, and

the United States reported on November 23 ahead of print in *Frontiers in Neurology* on a study using ^{18}F -FDG PET to characterize regional brain metabolic differences in patients with epilepsy at high risk of sudden unexpected death. The study included patients with refractory focal epilepsy at high ($n = 56$) and low ($n = 69$) risk of sudden unexpected death who underwent interictal ^{18}F -FDG PET as part of presurgical assessment. Whole-brain analyses were used to explore regional differences in interictal metabolic patterns and were contrasted with regional brain metabolism more directly related to frequency of focal-to-bilateral tonic-clonic seizures. Imaging found that regions associated with cardiorespiratory and somatomotor regulation differed in interictal metabolism. Tracer uptake was increased in the basal ganglia, ventral diencephalon, midbrain, pons, and deep cerebellar nuclei in patients in the high-risk of sudden death group, and uptake was decreased in the left planum temporale. These patterns differed from those associated with focal-to-bilateral tonic-clonic seizure frequency (decreased uptake in bilateral medial superior frontal gyri, extending into the left dorsal anterior cingulate cortex). PET-identified changes in interictal metabolic activity in regions critical to cardiorespiratory and somatomotor regulation in patients considered to be at relatively high risk of sudden death from epilepsy have the potential to elucidate processes that may predispose such patients to sudden death and to identify such patients and affect management.

Frontiers in Neurology

Benzodiazepine and AD: ^{18}F -Florbetapir PET and MRI

In an article published on December 10 ahead of print in *Neuropsychopharmacology*, Gallet, from University Hospital (Angers, France), and French re-searchers in the MEMENTO study looked at data from that cohort correlating benzodiazepine (BZD) use and neuroimaging markers of Alzheimer disease (AD) in nondemented older individuals with isolated memory complaints or light cognitive impairment at baseline. The study's goals were to replicate/assess findings on

BZD use and brain amyloid load with ^{18}F -florbetapir PET and to investigate associations between BZD use and hippocampal volume with MRI. Chronic BZD user and nonuser data on multiple-variable clinical, symptomatic, and genetic data were compared. The authors found that BZD users were more likely to manifest symptoms of depression, anxiety, and apathy. Total SUV ratios and hippocampal volumes were significantly lower and larger, respectively, in BZD users than in nonusers. Short-acting BZDs and Z-drugs (Zopiclone/Zolpidem) were more significantly associated with larger hippocampal volumes, with no significant effects associated with dose and duration of BZD use. The authors concluded that these results "support the involvement of the GABAergic system as a potential target for blocking AD-related pathophysiology, possibly via reduction in neuronal activity and neuro-inflammation" and noted that additional longitudinal studies may confirm the causal effect of BZDs in blocking amyloid accumulation and hippocampal atrophy.

Neuropsychopharmacology

DCE CT vs PET in Solitary Pulmonary Nodules

Gilbert, from the University of Cambridge (UK), and a large group of UK researchers reported on December 9 ahead of print in *Thorax* on a study comparing the accuracy and cost effectiveness of dynamic contrast-enhanced CT (DCE CT) and PET/CT in diagnosis of malignancy in solitary pulmonary nodules. The prospective multicenter trial included individuals with a solitary pulmonary nodule (range, 8–30 mm) and no recent history of malignancy. The protocol included both types of imaging and either biopsy with histologic diagnosis or completed CT follow-up. A total of 312 participants (53% men, 47% women; ages, 68.1 ± 9.0 y) completed the study, with a 61% rate of malignancy at 2-y follow-up. The sensitivity, specificity, and positive- and negative-predictive values for DCE-CT were 95.3%, 29.8%, 68.2%, and 80.0%, respectively. For PET/CT the respective percentages were 79.1%, 81.8%, 87.3%, and 71.2%. The areas under the receiver

operator characteristic curves for DCE-CT and PET/CT were 0.62 and 0.80, respectively. Combining results from the 2 imaging modalities significantly increased diagnostic accuracy over PET/CT alone. In a cost analysis, DCE-CT was preferred when the “willingness to pay” per incremental cost per correctly treated malignancy was below £9,000. Above £15,500 a combined approach was preferred. The authors concluded that “PET/CT has a superior diagnostic accuracy to DCE-CT for the diagnosis of solitary pulmonary nodules” and that “combining both techniques improves the diagnostic accuracy over either test alone and could be cost effective.”

Thorax

PET/CT Textural Features in Follicular Lymphoma

In an article published in the December 10 issue of *Scientific Reports* (2021;11[1]:23812), Faudemer et al. from Caen University Hospital, Normandy University (Caen), and the Comprehensive Cancer Centre François Baclesse (Caen; all in France) reported on a study assessing the value of baseline ^{18}F -FDG PET/CT radiomics (skeletal textural features) in the diagnosis of bone marrow involvement in patients with follicular lymphoma. The retrospective study included 66 patients newly diagnosed with follicular lymphoma. For visual assessment, patients with obvious bone focal uptake were considered positive. For textural analysis, skeletal volumes of interest were automatically extracted from segmented CT images. Bone marrow biopsy and visual assessment were used as a gold standard in categorizing participants as bone-negative (negative bone marrow biopsy/negative PET) or bone-positive (positive bone marrow biopsy/negative PET, negative bone marrow biopsy/positive PET, or positive bone marrow biopsy/positive PET). Thirty-six patients (54.5%) were classified as bone-negative and 30 (45.5%) as bone-positive. Software analysis identified a cut-off of -0.190 as optimal for diagnosis of bone marrow involvement using a PET predictive score. The corresponding sensitivity, specificity, and positive- and negative-predictive values for PET were

70.0%, 83.3%, 77.8%, and 76.9%, respectively. A significant difference was found between bone marrow biopsy results and visual PET assessments, whereas bone marrow biopsy results and the PET radiomics predictive score were concordant. The authors concluded that “skeleton texture analysis is worth exploring to improve the performance of ^{18}F -FDG PET/CT for the diagnosis of bone marrow involvement at baseline in follicular lymphoma patients.”

Scientific Reports

PET/CT Prediction of Urinary Retention After Hysterectomy

Davidson et al. from Chaim Sheba Medical Center (Tel Hashomer), Tel Aviv University (Ramat Aviv), and Hebrew University of Jerusalem (all in Israel) reported on December 14 ahead of print in *Minerva Obstetrics and Gynecology* on a study using ^{18}F -FDG PET/CT to measure residual urinary volume both before and after radical hysterectomy to determine whether scanned abnormal residual bladder volume is predictive of future urinary symptoms. The study included 64 women. Postvoid bladder volumes were $\geq 150\text{ cm}^3$ on postoperative PET/CT in 24 (38%) patients, with 9 (37.5%) of these experiencing some degree of voiding difficulty. In 3 of the 24 patients, the high bladder volume on PET/CT was seen 2–4 mo before complaints of voiding difficulty. Of the 40 (62%) remaining patients whose postoperative bladder volumes were $< 150\text{ cm}^3$, only 1 (2.5%) had urinary retention. Symptomatic voiding difficulties were higher in the postvoid volume $\geq 150\text{ cm}^3$ group than in the $< 150\text{ cm}^3$ group (13 and 6, respectively). The authors concluded that “measuring bladder volume on postoperative ^{18}F -FDG PET/CT may facilitate early identification of urinary retention, possibly enabling early treatment and possibly preventing complications.”

Minerva Obstetrics and Gynecology

Machine Learning and SPECT MPI Polar Maps

In an article published on November 11 in *Frontiers in Cardiovascular*

Medicine (2021;8:741667), Marques de Souza Filho et al. from the Universidade Federal Fluminense (Rio de Janeiro, Brazil), Universidade Federal Rural do Rio de Janeiro (Rio de Janeiro, Brazil), the University of Ottawa Heart Institute (Canada), and the Hospital Pró-Cardíaco/Americas Serviços Médicos (Rio de Janeiro, Brazil) reported on a study using machine learning algorithms to differentiate normal from abnormal gated SPECT myocardial perfusion polar map images. The authors analyzed 1,007 polar maps from a database of patients referred for clinically indicated myocardial perfusion imaging. Studies were first visually assessed and reported by experts as a comparative standard. Image features were then extracted using polar map segmentation based on horizontal and vertical slices. Cross-validation divided the dataset into training and testing subsets. All machine learning models (except for 1) had accuracy $> 90\%$ and area under the receiver operating characteristics curves > 0.80 . Overall machine learning precision and sensitivity were $> 96\%$ and 92% , respectively. The authors concluded that machine learning algorithms performed well in image classification and were remarkably capable of distinguishing normal from abnormal polar maps.

Frontiers in Cardiovascular Medicine

Nanoparticle Radioenhancer Plus RIT

Hu et al. from the University of Texas MD Anderson Cancer Center (Houston, TX), Nanobiotix (Paris, France), the Shandong Cancer Hospital and Institute/Shandong First Medical University/Shandong Academy of Medical Sciences (Jinan, China), and the Koc University School of Medicine (Istanbul, Turkey) reported on December 11 in the *Journal of Nanobiotechnology* (2021;19[1]:416) on results from a study of multicomination therapy in which NBTXR3, a clinically approved nanoparticle radioenhancer, was combined with high-dose radiation to a primary tumor plus low-dose radiation to a secondary tumor along with

immune checkpoint inhibitor blockade in a mouse model of anti-PD1-resistant metastatic lung cancer. In the complex protocol, mice were injected with a metastatic mouse lung cancer cell line in the right leg on d 0 for the primary tumor and the left leg on d 3 for the secondary tumor. Immune checkpoint inhibitors (anti-PD1 and anti-CTLA4) were administered intraperitoneally. Primary tumors were injected with NBTXR3 on d 6 and irradiated with 12 Gy on d 7, 8, and 9. Secondary tumors were irradiated with 1 Gy on d 12 and 13. Surviving mice at d 178 were rechallenged with the original lung cancer cell lines, and tumors were monitored. The researchers found that the combination of therapies resulted in significant antitumor effects against both primary and secondary tumors, improving the survival rate from 0 to 50%. Immune profiling in secondary tumors showed that the nanoparticle enhancer plus low- and high-dose radiation increased CD8 T-cell infiltration and decreased the number of regulatory T cells. None of the rechallenged mice developed tumors. These rechallenged mice were found to have higher percentages of CD4 memory T cells and CD4 and CD8 T cells in both blood and spleen than untreated mice. The authors concluded that the NBTXR3 nanoparticle “in combination with radioimmunotherapy significantly improves anti-PD1-resistant lung tumor control via promoting antitumor immune response.”

Journal of Nanobiotechnology

Coffee Consumption and Cognitive Decline

Gardener, from Edith Cowan University (Joondalup, Australia), and a consortium of researchers from the Australian Imaging, Biomarkers, and Lifestyle (AIBL) study reported on November 19 in *Frontiers in Aging Neuroscience* (2021;13:744872) on the results of an investigation of the relationship between self-reported habitual coffee intake and cognitive decline. The report included AIBL data with comprehensive neuropsychological battery assessments from 227 cognitively normal older adults over more than 10 y. The researchers also investigated the relationship between habitual coffee intake and

cerebral amyloid- β accumulation in 60 of the individuals and brain volumes in 51. The researchers found that higher baseline coffee consumption was associated with slower cognitive decline in executive function, attention, and performance on the AIBL Preclinical Alzheimer Disease Cognitive Composite assessment and with lower likelihood of transitioning to mild cognitive impairment or AD status over the duration of the study. Higher baseline coffee consumption was also associated with slower amyloid- β accumulation and lower risk of progressing to moderate, high, or very high categories of amyloid- β burden. No associations were noted between coffee intake and atrophy in total gray matter, white matter, or hippocampal volumes. The authors concluded that these results “support the hypothesis that coffee intake may be a protective factor against Alzheimer disease, with increased coffee consumption potentially reducing cognitive decline by slowing cerebral A β -amyloid accumulation, and thus attenuating the associated neurotoxicity from A β -amyloid-mediated oxidative stress and inflammatory processes.”

Frontiers in Aging Neuroscience

Delayed PET and Glioblastoma Conspicuity

In an article in the November 16 issue of *Frontiers in Neurology* (2021; 12:740280), Johnson et al. from the University of Texas MD Anderson Cancer Center and Baylor College of Medicine (both in Houston, TX) reported on a study designed to determine the ideal timepoint for ^{18}F -FDG PET imaging of suspected glioblastoma. The study was intended as part of preparation for future trials involving noninvasive differentiation of true progression from pseudoprogression in glioblastoma. This initial investigation included 16 adults (9 men, 7 women) with suspected glioblastoma who underwent PET imaging at 1, 5, and 8 h after ^{18}F -FDG injection within 3 d before scheduled surgery. Maximum SUVs were quantified for the central enhancing component of the lesion and contralateral normal brain. Results showed statistically significant improvements in maximum SUVs and subjective reader

conspicuity of glioblastomas at later time points when compared to the conventional 1-h time point. Tumor-to-background ratios at 1, 5, and 8 h after tracer injection were 1.4 ± 0.4 , 1.8 ± 0.5 , and 2.1 ± 0.6 , respectively. The authors concluded that these findings “demonstrate that delayed imaging time point provides superior conspicuity of glioblastoma compared to conventional imaging.”

Frontiers in Neurology

Characterizing BRAF-Mutant Papillary Thyroid Cancer Subtypes

Boucai et al. from the Memorial Sloan Kettering Cancer Center (New York, NY), MD Anderson Cancer Center (Houston, TX), and the Cleveland Clinic (OH) reported on November 23 online ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on a study looking at the feasibility of characterizing the molecular and clinical features of 2 subtypes of BRAF-mutant papillary thyroid cancer by their degree of expression of iodine metabolism genes. The study included data from 227 BRAF-mutant papillary thyroid cancer tumors in the Cancer Genome Atlas (Thyroid Cancer), divided into 2 subgroups based on their thyroid differentiation score (TDS; categorized as high or low). A range of data points were compared between the 2 groups. Seventeen percent of tumors were categorized as high BRAF-TDS and 83% as low. High BRAF-TDS tumors were more common in black and Hispanic patients. High BRAF-TDS tumors were also larger, associated with more tumor-involved lymph nodes, and had a higher frequency of distant metastases. Gene set enrichment analyses showed positive enrichment for RAS signatures in the high BRAF-TDS cohort, with corresponding but less pronounced changes in the low group. Several microRNAs (miR-204, miR-205, and miR-144) were overexpressed in the high group. In a subset of data on clinical patient follow-up, those with high BRAF-TDS tumors had higher complete responses to therapy than those in the low BRAF-TDS tumor group

(94% and 57%, respectively). The authors concluded that “enrichment for RAS signatures, key genes involved in cell polarity, and specific miRs targeting the transforming growth factor β –SMAD pathway define 2 subtypes of BRAF-mutant papillary thyroid cancer subtypes with distinct clinical characteristics and prognosis.”

Journal of Clinical Endocrinology and Metabolism

SLN Visualization in Upper Urinary Tract Urothelial Cancer

In an article published on November 23 in the *Journal of Clinical Medicine* (2021;10[23]:5465), Polom et al. from the Medical University of Gdansk (Poland) reported on a radioisotope-based technique for detection of sentinel lymph nodes (SLNs) and analysis of lymphatic outflow in patients with suspected upper-tract urothelial carcinoma (UTUC). The study included 19 such patients (7 men, 12 women; mean age, 73.4 y) who were scheduled for ureterorenoscopy. Staging included ^{99m}Tc -nanocolloid radioactive tracer injection and tumor biopsy (pathology: 8 patients, T0 [42%]; 7 patients, Ta [36%]; and 4 patients, T1 [21%]). 3D reconstruction and image fusion were performed for better localization of lymph nodes, and SPECT/CT lymphangiography was used for detection of SLNs and analysis of radiotracer outflow. SLNs were detected in 2 patients (10%): 1 in whom a single SLN was visualized and another in

whom multiple radioactive lymph nodes were visualized. SPECT/CT detected no lymphatic outflow in 17 (89.5%) patients. In 5 of these patients (26.3%), however, gravitational leakage of injected radiotracer to the retroperitoneal space was noted. The authors concluded that these results reinforce the challenging nature of detecting SLNs in the upper urinary tract, with associated difficulties in radiotracer injection during ureterorenoscopy. However, “SPECT/CT lymphangiography in cases of UTUC may provide valuable information about a patient's individual anatomy of the lymphatic system and the position of the first lymph nodes draining lymph with potential metastatic cells from the tumor.”

Journal of Clinical Medicine

Reviews

Review articles provide an important way to stay up to date on the latest topics and approaches through valuable summaries of pertinent literature. The Newsline editor recommends several general reviews accessioned into the PubMed database in November and December. Rowe and Pomper, from the Johns Hopkins University School of Medicine (Baltimore, MD), provided an overview of “Molecular imaging in oncology: Current impact and future directions” on December 13 ahead of print in *CA: A Cancer Journal for Clinicians*. In an article in the November 30 issue of *Cancers (Basel)* (2021;13:6026), Guglielmo

et al. from the Veneto Institute of Oncology IOV-IRCCS and the University of Padova (both in Italy) surveyed the “Additional value of PET radiomic features for the initial staging of prostate cancer: A systematic review from the literature.” The role of “Tau biomarkers in dementia: Positron emission tomography radiopharmaceuticals in tauopathy assessment and future perspective” was outlined by Ricci et al. from the University of Rome Tor Vergata and IRCCS Neuromed (Pozzilli; both in Italy) in the November 30 issue of the *International Journal of Molecular Sciences* (2021; 22[23]:13002). Beuthien-Baumann et al. from the Deutsches Krebsforschungszentrum Heidelberg and the Universitätsklinikum Heidelberg (both in Germany) reviewed “Adapting imaging protocols for PET-CT and PET-MRI for immunotherapy monitoring” in the November 30 issue of *Cancers (Basel)* (2021; 13[23]:6019). In the November 24 issue of *Molecules* (2021;26[23]:7111) Prigent and Vigne from Normandie Université (Caen, France) outlined “Advances in radiopharmaceutical sciences for vascular inflammation imaging: Focus on clinical applications.” Rondon et al. from the Université Catholique de Louvain (Brussels, Belgium), the Université Clermont-Auvergne (Clermont-Ferrand, France), and CHU Estaing (Clermont-Ferrand, France) published “Radioimmunotherapy in oncology: Overview of the last decade clinical trials” on November 7 in *Cancers (Basel)* (2021;13[21]:5570).