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Henry Ford Health System

Henry Ford Health System Publication List – November 2021

This bibliography aims to recognize the scholarly activity and provide ease of access to journal articles, meeting abstracts, book chapters, books and other works published by Henry Ford Health System personnel. Searches were conducted in PubMed, Embase, and Web of Science during the month, and then imported into EndNote for formatting. There are **144 unique citations** listed this month, with **9 articles** and **1 conference abstract on COVID-19**. Articles are listed first, followed by conference abstracts, books and book chapters, and a bibliography of publications on COVID-19. Because of various limitations, this does not represent an exhaustive list of all published works by Henry Ford Health System authors.

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Articles

Conference Abstracts

Articles

Administration
Maceri J. Positive outcomes of a surgical progressive care unit for patients following head and neck cancer surgery. *Nurs Manage* 2021; 52(11):34-40. PMID: 34723884. Full Text

Jocelyn Maceri is a nursing administrator at Henry Ford Hospital in Detroit, Mich.

Allergy and Immunology
Johnson CC, **Havstad SL**, Ownby DR, **Joseph CLM**, **Sitarik AR**, Biagini Myers J, Gebretsadik T, Hartert TV, Khurana Hershey GK, Jackson DJ, Lemanske RF, Jr., Martin LJ, **Zoratti EM**, Visness CM, Ryan PH, Gold DR, Martinez FD, Miller RL, Seroogy CM, Wright AL, and Gern JE. Pediatric asthma incidence rates in the United States from 1980 to 2017. *J Allergy Clin Immunol* 2021; 148(5):1270-1280. PMID: 33964299. Full Text

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Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wis.
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Asthma and Airways Research Center, University of Arizona, Tucson, Ariz; Division of Pulmonary and Sleep Medicine, Department of Pediatrics, College of Medicine, University of Arizona, Tucson, Ariz.
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BACKGROUND: Few studies have examined longitudinal asthma incidence rates (IRs) from a public health surveillance perspective. OBJECTIVE: Our aim was to calculate descriptive asthma IRs in children over time with consideration for demographics and parental asthma history. METHODS: Data from 9 US birth cohorts were pooled into 1 population covering the period from 1980 to 2017. The outcome was earliest parental report of a doctor diagnosis of asthma. IRs per 1,000 person-years were calculated. RESULTS: The racial/ethnic backgrounds of the 6,283 children studied were as follows: 55% European American (EA), 25.5% African American (AA), 9.5% Mexican-Hispanic American (MA) and 8.5% Caribbean-Hispanic American (CA). The average follow-up was 10.4 years (SD = 8.5 years; median = 8.4 years), totaling 65,291 person-years, with 1789 asthma diagnoses yielding a crude IR of 27.5 per 1,000 person-years (95% CI = 26.3-28.8). Age-specific rates were highest among children aged 0 to 4 years, notably from 1995 to 1999, with a decline in EA and MA children in 2000 to 2004 followed by a decline in AA and CA children in 2010 to 2014. Parental asthma history was associated with statistically significantly increased rates. IRs were similar and higher in AA and CA children versus lower but similar in EA and MA children. The differential rates by sex from birth through adolescence principally resulted from a decline in rates among males but relatively stable rates among females. CONCLUSIONS: US childhood asthma IRs varied dramatically by age, sex, parental asthma history, race/ethnicity, and calendar year. Higher rates in the 0- to 4-year-olds group, particularly among AA/CA males with a parental history of asthma, as well as changes in rates over time and by demographic factors, suggest that asthma is driven by complex interactions between genetic susceptibility and variation in time-dependent environmental and social factors.

Allergy and Immunology
Joseph CL, **Sitarik AR**, **Kim H**, Huffnagle G, Fujimura K, Yong GJM, **Levin AM**, **Zoratti E**, Lynch S, Ownby DR, Lukacs NW, Davidson B, **Barone C**, and **Cole Johnson C**. Infant gut bacterial community composition and food-related manifestation of atopy in early childhood. *Pediatr Allergy Immunol* 2021; Epub ahead of print. PMID: 34811824. Full Text

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BACKGROUND: Immunoglobulin E - mediated food allergy (IgE-FA) has emerged as a global public health concern. Immune dysregulation is an underlying mechanism for IgE-FA, caused by "dysbiosis" of the early intestinal microbiota. We investigated the association between infant gut bacterial composition and food-related atopy at age 3-5 years using a well-characterized birth cohort. METHODS: The study definition of IgE-FA to egg, milk, or peanut was based on physician panel retrospective review of clinical and questionnaire data collected from birth through age 3-5 years. Using 16S rRNA sequencing, we profiled the bacterial gut microbiota present in stool specimens collected at 1 and 6 months of age. RESULTS: Of 447 infants with data for analysis, 44 (9.8%) met physician panel review criteria for IgE-FA to ≥1 of the three allergens. Among children classified as IgE-FA at 3-5 years, infant stool samples showed significantly less diversity of the gut microbiota compared to the samples of children classified as no IgE-FA at age 3-5 years, especially for milk and peanut (all covariate adjusted p's for alpha metrics <0.007). Testing of individual operational taxonomic units (OTUs) revealed 6-month deficiencies in 31 OTUs for IgE-FA compared to no IgE-FA, mostly in the orders Lactobacillales, Bacteroidales, and Clostridiales. CONCLUSIONS: Variations in gut microbial composition in infant stool were associated with a study definition of IgE-FA at 3-5 years of age. This included evidence of a lack of bacterial diversity, deficiencies in specific OTUs, and delayed microbial maturation. Results support dysbiosis in IgE-FA pathogenesis.

Anesthesiology
Allos MT, **Zukowski DM**, and **Fidkowski CW**. Erector Spinae Plane Continuous Catheters for Refractory Abdominal Pain Related to Necrotizing Pancreatitis: A Case Report. *A A Pract* 2021; 15(11). PMID: 34752440. Full Text

From the Department of Anesthesiology, Pain Management, and Perioperative Medicine, Henry Ford Hospital, Detroit, Michigan.

Erector spinae plane (ESP) continuous catheters are used for the management of postsurgical pain. The use of these catheters for acute nonsurgical abdominal pain is not well defined. This case describes a patient with refractory abdominal pain secondary to necrotizing pancreatitis despite escalating doses of opioids, ketamine, and dexmedetomidine. Our patient declined epidural analgesia. Bilateral ESP continuous catheters successfully controlled her pain, and she was weaned off of all analgesics during the week following catheter placement. This case demonstrates that ESP continuous catheters can be considered for patients with acute nonsurgical abdominal pain especially when thoracic epidural analgesia is contraindicated.

Anesthesiology
Cook A, Modh A, **Ali H**, **Sheqwara J**, **Chang S**, **Ghanem T**, **Momin S**, **Wu V**, **Tam S**, **Money S**, **Han X**, **Fakhoury L**, **Movsas B**, and **Siddiqui F**. Randomized Phase III, Double Blind, Placebo-Controlled Study of Prophylactic Gabapentin for the Reduction of Oral Mucositis Pain During the Treatment of Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; Epub ahead of print. PMID: 34808255. Full Text

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PURPOSE: To determine if prophylactic gabapentin usage in patients undergoing definitive concurrent chemoradiotherapy (chemoRT) for oropharyngeal cancer (OPC) improves treatment-related oral mucositis pain, opioid use, and feeding tube (FT) placement. METHODS AND MATERIALS: This double-blind, randomized phase III study for patients with locally advanced OPC undergoing chemoRT randomly allocated patients to prophylactic gabapentin (600 mg thrice daily) or placebo. The primary endpoint was change in Patient-Reported Oral Mucositis Symptom (PROMS) scores over the entire treatment period (baseline to 6 weeks post-RT follow-up) with higher scores indicating worse outcomes. Opioid requirements, FT placement, and other patient-reported QOL metrics (Functional Assessment of Cancer Therapy-Head and Neck [FACT-HN] and Patient-Reported Outcomes of Common Terminology Criteria for Adverse Events [PRO-CTCAE]) were assessed. Lower scores suggested poorer quality of life (QOL) with the FACT-HN questionnaire, and higher scores suggested worse outcomes with the PRO-CTCAE questionnaire. Questionnaires were administered at baseline, weekly during RT, and at 6-week post-RT follow-up. Repeated measures analysis of variance were used to detect differences in PROMS scores and change in opioid use from baseline. Wilcoxon-rank sum tests were used to compare averages for the other secondary endpoints. A p-value less than .05 was considered statistically significant. RESULTS: Treatment arms were well-balanced overall, including T and N staging and dosimetric variables. There were 58 patients analyzed. No significant difference was found in PROMS scores (mean 29.1, Standard Deviation [SD] 22.5, vs 20.1, SD 16.8, for gabapentin vs placebo, respectively, p = .11). The FACT-HN functional well-being index had a significant decrease in scores from baseline to follow-up in the gabapentin arm (median -6, interquartile range [IQR] -10.0 to -0.5, vs -1, IQR -5.5 to 3.0, p = .03). PRO-CTCAE scores increased significantly at follow-up for gabapentin (median 6.5, IQR 3.5 to 11.8, vs 1, IQR -2.0 to 6.0, p = .01). There was no significant difference in average or change in opioid use. FT placement was significantly higher in the gabapentin arm (62.1% vs 20.7%, p < .01). CONCLUSIONS: This study suggests that prophylactic gabapentin is not effective in improving treatment-related oral mucositis symptoms in a select population of patients with OPC undergoing definitive chemoRT.

Anesthesiology

Fayed M, **Patel N**, **Yeldo N**, **Nowak K**, **Penning DH**, **Vasconcelos Torres F**, **Natour AK**, and **Chhina A**. Effect of Intubation Timing on the Outcome of Patients With Severe Respiratory Distress Secondary to COVID-19 Pneumonia. *Cureus* 2021; 13(11). PMID: 34804753. Full Text

Anesthesiology, Pain Management and Perioperative Medicine, Henry Ford Health System, Detroit, USA.
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Background The optimal timing of intubation for critically ill patients with severe respiratory illness remains controversial among healthcare providers. The coronavirus disease 2019 (COVID-19) pandemic has raised even more questions about when to implement this life-saving therapy. While one group of providers prefers early intubation for patients with respiratory distress because these patients may deteriorate rapidly without it, other providers believe that intubation should be delayed or avoided because of its associated risks including worse outcomes. Research question Our objective was to assess whether the timing of intubation in patients with severe COVID-19 pneumonia was associated with differences in mortality or other outcomes. Study design and methods This was a single-center retrospective observational cohort study. We analyzed outcomes of patients who were intubated secondary to COVID-19 pneumonia between March 13, 2020, and December 12, 2020, at Henry Ford Hospital in Detroit, Michigan. Patients were categorized into two groups: early intubated (intubated within 24 hours of the onset of severe respiratory distress) and late intubated (intubated after 24 hours of the onset of severe respiratory distress). Demographics, comorbidities, respiratory rate oxygenation (ROX) index, sequential organ failure assessment (SOFA) score, and treatment received were compared

between groups. The primary outcome was mortality. Secondary outcomes were ventilation time, intensive care unit stay, hospital length of stay, and discharge disposition. Post hoc and Kaplan-Meier survival analyses were performed. Results A total of 110 patients were included: 55 early intubated and 55 late intubated. We did not observe a significant difference in overall mortality between the early intubated (43%) and the late intubated groups (53%) ($p = 0.34$). There was no statistically significant difference in patients' baseline characteristics including SOFA scores (the early intubation group had a mean score of 7.5 compared to 6.7 in the late intubation group). Based on the ROX index, the early intubation group had significantly more patients with a reduced risk of intubation (45%) than the late group (27%) ($p = 0.029$). The early intubation group was treated with a high-flow nasal cannula at a significantly lower rate (47%) than the late intubation group (83%) ($p < 0.001$). Significant differences in patient baseline characteristics, treatment received, and other outcomes were not observed. Post hoc analysis adjusting for SOFA score between 0 and 9 revealed significantly higher mortality in the late intubation group (49%) than in the early intubation group (26%) ($p = 0.03$). Patients in the 0 to 9 SOFA group who were intubated later had 2.7 times the odds of dying during hospital admission compared to patients who were intubated early (CI, 1.09-6.67). Interpretation The timing of intubation for patients with severe COVID-19 pneumonia was not significantly associated with overall mortality or other patient outcomes. However, within the subgroup of patients with SOFA scores of 9 or lower at the time of intubation, patients intubated after 24 hours of the onset of respiratory distress had a higher risk of death than those who were intubated within 24 hours of respiratory distress. Thus, patients with COVID-19 pneumonia who are not at a high level of organ dysfunction may benefit from early mechanical ventilation.

Anesthesiology

Fayed M, Pusapati R, Widdicombe N, Sypek M, **Ibrahim R**, **Yeldo N**, and **Penning DH**. Characteristics of Organ Donors Who Died From Suicide by Hanging in Australia and New Zealand: A Retrospective Study. *Cureus* 2021; 13(11). PMID: 34754703. Full Text

Anesthesiology, Henry Ford Health System, Detroit, USA.
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Background and objective The annual incidence of suicide by hanging in Australia and New Zealand has increased in the past decade, and a significant number of these individuals are becoming organ donors. The rates of organ donation following deaths from hanging is unknown and the characteristics of this cohort of donors have not been described in the literature. In light of this, we aimed to examine the trends in organ donation from individuals who had died from hanging, based on the solid organ donor data from the Australia and New Zealand Organ Donation (ANZOD) Registry. Methods We conducted a retrospective study that analyzed the ANZOD Registry donor data (2006-2015) to describe the characteristics of solid organ donors who had died by hanging (post-hanging group); these characteristics were compared to those of individuals who died by all other causes (non-hanging group). Results During the study period, the number and proportion of donors who died by suicide from hanging increased. Of the 4,024 consented organ donors, 226 had died by hanging and 3,798 had died from other causes. The probability that an individual who died by hanging would become an organ donor increased from 0.5 to 3%. Compared to donors who died by all other causes, post-hanging donors were younger (median age of 30 vs. 50 years), with fewer comorbidities, and a higher incidence of smoking. There was no significant difference in the proportion of those who indicated a prior intent to donate organs between post-hanging (34%) and non-hanging donors (38%). A higher proportion of post-hanging donors donated via the donation after the circulatory death pathway (36.3%) than non-hanging donors (24.2%). Individuals in the post-hanging cohort donated an average of 4.19 organs compared to 3.62 in the non-hanging cohort. Conclusion We believe the findings of this retrospective analysis will help inform clinical decision-making regarding organ donation, including the best approaches to obtaining donation consent. Our findings will help physicians provide care to patients and to families of individuals in this challenging group, where organ donation potential is high. Further investigations are required to determine which aspects of healthcare influence the donation rates in individuals who have died by hanging and the outcomes related to transplanted organs.

Anesthesiology

Rivas E, Cohen B, Pu X, Xiang L, **Saasouh W**, Mao G, Minko P, Mosteller L, Volio A, Maheshwari K, Sessler DI, and Turan A. Pain and Opioid Consumption and Mobilization after Surgery: Post Hoc Analysis of Two Randomized Trials. *Anesthesiology* 2021; Epub ahead of print. PMID: 34780602. Full Text

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BACKGROUND: Early mobilization is incorporated into many enhanced recovery pathways. Inadequate analgesia or excessive opioids may restrict postoperative mobilization. The authors tested the hypotheses that in adults recovering from abdominal surgery, postoperative pain and opioid consumption are inversely related to postoperative mobilization, and that postoperative mobilization is associated with fewer potentially related complications. METHODS: The authors conducted a subanalysis of two trials that enrolled adults recovering from abdominal surgery. Posture and movement were continuously monitored for 48 postoperative hours using noninvasive untethered monitors. Mobilization was defined as the fraction of monitored time spent sitting or standing. RESULTS: A total of 673 patients spent a median [interquartile range] of 7% [3 to 13%] of monitored time sitting or standing. Mobilization time was 1.9 [1.0 to 3.6] h/day for patients with average pain scores 3 or lower, but only 1.2 [0.5 to 2.6] h/day in those with average scores 6 or greater. Each unit increase in average pain score was associated with a decrease in mobilization time of 0.12 (97.5% CI, 0.02 to 0.24; P = 0.009) h/day. In contrast, there was no association between postoperative opioid consumption and mobilization time. The incidence of the composite of postoperative complications was 6.0% (10 of 168) in the lower mobilization quartile, 4.2% (7 of 168) in the second quartile, and 0% among 337 patients in the highest two quartiles (P = 0.009). CONCLUSIONS: Patients recovering from abdominal surgery spent only 7% of their time mobilized, which is considerably less than recommended. Lower pain scores are associated with increased mobility, independently of opioid consumption. Complications were more common in patients who mobilized poorly.

Behavioral Health Services/Psychiatry/Neuropsychology

Felton JW, Schwartz KTG, Oddo LE, Lejuez CW, and Chronis-Tuscano A. Transactional patterns of depressive symptoms between mothers and adolescents: The role of emotion regulation. *Depress Anxiety* 2021; Epub ahead of print. PMID: 34762765. Full Text

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BACKGROUND: Depression is a highly prevalent, debilitating disorder that runs in families. Yet, empirical support for bidirectional mechanisms linking mother-adolescent depression symptoms remains limited. This study examined longitudinal bidirectional relations among emotion regulation (ER) constructs and depressive symptoms among mother-adolescent dyads over time. Pathways for girls and boys were explored separately, given extant research on sex differences in the intergenerational transmission of depression. METHODS: Adolescent (n = 232; M = 15.02 years, SD = 0.95; 44% female)-mother dyads, drawn from a longitudinal study on the development of risky behaviors, completed annual assessments of depressive symptoms and facets of ER over 4 years. Panel modeling examined lagged and cross-lagged effects of mother-adolescent depressive symptoms and ER constructs over time, in a multigroup model of boys and girls. RESULTS: Among girls, higher baseline maternal depression scores predicted increased adolescent ER difficulties (std. est. = -.42, p < .001) in turn, predicting increased adolescent depressive symptoms (std. est. = -.33, p = .002) and subsequent maternal ER difficulties (std. est. = .39, p = .002). The indirect effect of maternal depressive symptoms→adolescent ER→adolescent depressive symptoms→maternal ER was significant (ind. eff. = .10, 95% confidence interval [>.001, .19]) for girls, but not boys. CONCLUSION: Implications for interrupting intergenerational cycles of depressive symptoms and emotion dysregulation are discussed.

Behavioral Health Services/Psychiatry/Neuropsychology
Gautam M, Kaur M, and **Sivananthan M**. Parotid Gland Enlargement Associated With Clonazepam: A Case Report. *J Acad Consult Liaison Psychiatry* 2021; 62(6):657-658. PMID: 34186253. Full Text

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Behavioral Health Services/Psychiatry/Neuropsychology
Martens K, Ulrich GR, Ranby KW, and Kilbourn K. What Matters Most? Predictors of Quality of Life and Life Satisfaction Among Young Breast Cancer Survivors. *Cancer Nurs* 2021; 44(6):E727-e734. PMID: 34694091. Full Text

Author Affiliations: Department of Bariatric Surgery & Behavioral Health Services, Henry Ford Health System (Dr Martens), Detroit, Michigan; and Department of Psychology, University of Colorado Denver (Ms Ulrich and Drs Ranby and Kilbourn).

BACKGROUND: Younger breast cancer survivors face unique challenges, and research is needed to better understand how to optimize their quality of life (QoL) and satisfaction with life (SwL). OBJECTIVE: The aim of this study was to examine a biopsychosocial model of QoL and SwL in young breast cancer survivors. Biological, psychological, and social/practical factors were hypothesized to be associated with both distressing and adaptive reactions during survivorship, which in turn were hypothesized to be associated with QoL and SwL. METHODS: Young (age = 19-45 years at diagnosis) breast cancer survivors (N = 284) completed an online survey assessing demographic and biopsychosocial factors, QoL, and SwL. Latent variables were created for adaptive and distressing reactions, and structural equation modeling was used to test the hypothesized relationships. RESULTS: The model fit the data ($\chi 2(100) = 332.92$, P < .001, comparative fit index = 0.86, root mean square error of approximation = 0.09, standardized root mean square residual = 0.05) and accounted for large proportions of variance in QoL (R2 = 0.86) and SwL (R2 = 0.62). Social support, parenting concerns, and fertility concerns each significantly predicted adjustment. Adaptive reactions positively predicted SwL ($\beta = 0.58$, P < .001) but not QoL. Distressing reactions negatively predicted SwL ($\beta = -0.26$, P < .01) and QoL ($\beta = -0.87$, P < .001). CONCLUSIONS: Adjustment in survivorship mediated the association of social support, parenting concerns, and fertility concerns on QoL and SwL in young breast cancer survivors. IMPLICATIONS FOR PRACTICE: To support the psychological adjustment of young breast cancer survivors, attention should be given to survivors' social context including survivors' available social support and their concerns about fertility and parenting.

Cardiology/Cardiovascular Research

Barker M, Abbas AE, Webb JG, Pibarot P, Sathananthan J, Brunner N, **Wang DD**, Wang J, Leon MB, and Wood DA. Standardized Invasive Hemodynamics for Management of Patients With Elevated Echocardiographic Gradients Post-Transcatheter Aortic Valve Replacement at Midterm Follow-Up. *Circ Cardiovasc Interv* 2021; Epub ahead of print. PMID: 34802254. Full Text

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Cardiology/Cardiovascular Research

Han D, Chen B, Gransar H, Achenbach S, **Al-Mallah MH**, Budoff MJ, Cademartiri F, Maffei E, Callister TQ, Chinnaiyan K, Chow BJW, DeLago A, Hadamitzky M, Hausleiter J, Kaufmann PA, Villines TC, Kim YJ, Leipsic J, Feuchtner G, Cury RC, Pontone G, Andreini D, Marques H, Rubinshtein R, Chang HJ, Lin FY, Shaw LJ, Min JK, and Berman DS. Prognostic significance of plaque location in non-obstructive coronary artery disease: from the CONFIRM registry. *Eur Heart J Cardiovasc Imaging* 2021; Epub ahead of print. PMID: 34791117. Full Text

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AIM: Obstructive coronary artery disease (CAD) in proximal coronary segments is associated with a poor prognosis. However, the relative importance of plaque location regarding the risk for major adverse cardiovascular events (MACE) in patients with non-obstructive CAD has not been well defined. METHODS AND RESULTS: From the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry, 4644 patients without obstructive CAD were included in this study. The degree of stenosis was classified as 0 (no) and 1-49% (non-obstructive). Proximal involvement was defined as any plaque present in the left main or the proximal segment of the left anterior descending artery, left circumflex artery, and right coronary artery. Extensive CAD was defined as segment involvement score of >4. During a median follow-up of 5.2 years (interquartile range 4.1-6.0), 340 (7.3%) MACE occurred. Within the non-obstructive CAD group (n = 2065), proximal involvement was observed in 1767 (85.6%) cases. When compared to non-obstructive CAD patients without proximal involvement, those with proximal involvement had an increased MACE risk (log-rank P = 0.033). Multivariate Cox analysis showed when compared to patients with no CAD, proximal non-obstructive CAD was associated with increased MACE risk [hazard ratio (HR) 1.90, 95% confidence interval (CI) 1.47-2.45, P < 0.001] after adjusting for extensive CAD and conventional cardiovascular risk factors; however, non-proximal non-obstructive CAD did not increase MACE risk (HR 1.26, 95% CI 0.79-2.01, P = 0.339). CONCLUSIONS: Independent of plaque extent, proximal coronary involvement was associated with increased MACE risk in patients with non-obstructive CAD. The plaque location information by coronary computed tomography angiography may provide additional risk prediction over CAD extent in patients with non-obstructive CAD.

Cardiology/Cardiovascular Research
Hennessey B, Nuñez-Gil IJ, **Villablanca P**, and Ramakrishna H. Initial Invasive or Conservative Strategy for Stable Coronary Disease: The ISCHEMIA Trial and Its Clinical Implications. *J Cardiothorac Vasc Anesth* 2021; 35(11):3151-3153. PMID: 34210591. Full Text

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Cardiology/Cardiovascular Research
Megaly M, **Basir MB**, Brilakis E, and **Alaswad K**. "Power Carlino": A Novel Method for Modifying Wire-Impenetrable Proximal Caps During Chronic Total Occlusion Revascularization. *JACC Cardiovasc Interv* 2021; 14(22):2521-2522. PMID: 34743898. Full Text

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Cardiology/Cardiovascular Research
Megaly M, Sedhom R, Elbadawi A, Saad M, Omer M, Brilakis ES, **Basir MB**, Jaffer FA, **Zaidan M**, **Alqarqaz M**, and **Alaswad K**. Trends and outcomes of utilization of thrombectomy during primary percutaneous coronary intervention. *Cardiovasc Revasc Med* 2021; Epub ahead of print. PMID: 34167914. Full Text

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BACKGROUND: To describe the national trends and outcomes of contemporary thrombectomy use for primary percutaneous coronary intervention (PCI) from 2016 to 2018. METHODS: We queried the Nationwide Readmission Database (NRD) from January 2016 to December 2018 to identify patients who underwent primary PCI and thrombectomy. We conducted a multivariate regression analysis to identify variables associated with in-hospital mortality and stroke in patients undergoing primary PCI and those who underwent thrombectomy. RESULTS: We identified 409,910 total hospitalizations who underwent primary PCI. Thrombectomy was used in 62,446 records (15.2%) with no change in the trend over the study period (p trend = 0.52). Thrombectomy was more utilized in patients who had more cardiogenic shock and use of mechanical circulatory devices. The overall incidence of in-hospital mortality and stroke were 5.6% and 1.1%, respectively. The incidence of in-hospital mortality (6.7% vs. 5.4%, $p < 0.001$) and strokes (1.3% vs. 1.0%, $p < 0.001$) were higher in the thrombectomy group. On multivariable regression analysis adjusting for high-risk features, thrombectomy was not independently associated with in-hospital mortality [1.036, 95% CI (0.993-1.080), $p = 0.100$], but was associated with a higher risk of stroke [OR 1.186, 95% CI (1.097-1.283), $p < 0.001$]. CONCLUSION: During primary PCI, thrombectomy was used in 1 of 6 cases, and its use has been stable over 2016-2018. The use of thrombectomy was associated with a higher risk of stroke, but not in-hospital death.

Cardiology/Cardiovascular Research

Megaly M, Zordok M, Mentias A, Chugh Y, Buttar RS, **Basir MB**, Burke MN, Karmpaliotis D, Azzalini L, **Alaswad K**, and Brilakis ES. Complications and failure modes of covered coronary stents: Insights from the MAUDE database. *Cardiovasc Revasc Med* 2021; Epub ahead of print. PMID: 34052127. Full Text

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BACKGROUND: Data on the mechanisms of failure of covered coronary stents [Graftmaster, PK Papyrus] are limited. METHODS: We queried the "Manufacturer and User Facility Device Experience" (MAUDE) database between August 2018 (when the PK Papyrus stent was FDA approved) and December 2020 for reports on covered coronary stents. RESULTS: We identified 299 reports in the MAUDE database (after excluding duplicates, peripheral vascular reports, and incomplete records) (Graftmaster n = 225, PK Papyrus n = 74). The most common mechanism of failure of covered stents was failure to deliver the stent (46.2%), followed by stent dislodgement (22.4%) and failure to seal the perforation (19.7%). Failure to deliver the stent was more often reported with Graftmaster compared with PK Papyrus (59.1% vs. 6.8%, $p < 0.001$). Stent dislodgement was more often reported with PK Papyrus

compared with Graftmaster (75.7% vs. 4.9%, p < 0.001) and was managed by device retrieval or by crushing the stent. CONCLUSIONS: The most common failure mechanisms of covered stents are failure of delivery, stent dislodgement, and failure to seal the perforation. Failure of delivery was more common with Graftmaster, while stent dislodgement was more common with PK Papyrus. Further improvements in covered stent design are needed to optimize deliverability and minimize the risk of complications.

Cardiology/Cardiovascular Research
Michaelis T, **Gunaga S**, **McKechnie T**, and **Shafiq Q**. Acute Myocardial Infarction in a Patient with Twin Pregnancy: A Case Report. *Clin Pract Cases Emerg Med* 2021; 5(4):507-510. PMID: 34813459. Full Text

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INTRODUCTION: Acute myocardial infarction (AMI) rarely occurs during pregnancy and presents unique challenges in diagnosis and management. Traditionally, pregnancy has not readily been considered a risk factor for AMI in the emergency department despite the potential for adverse impacts on maternal and fetal health. As cardiovascular risk factors and advanced maternal age become more prevalent in society over time, the incidence will continue to increase. Prior cases with singular gestation have been reported; however, only one previous case during a twin pregnancy was identified in the medical literature. CASE REPORT: We describe a rare case of acute ST-segment elevation myocardial infarction in a 37-year-old woman at 24 weeks gestation with a dichorionic diamniotic twin pregnancy. CONCLUSION: It is important for the emergency physician to recognize acute coronary syndrome as a part of the differential diagnosis of chest pain in pregnant patients and be familiar with the diagnostic and management options available for this special population.

Cardiology/Cardiovascular Research
Nikolakopoulos I, Vemmou E, Xenogiannis I, Karacsonyi J, Rao SV, Romagnoli E, Tsigkas G, Milkas A, Velagapudi P, **Alaswad K**, Rangan BV, Garcia S, Burke MN, and Brilakis ES. Radial versus femoral access in patients with coronary artery bypass surgery: Frequentist and Bayesian meta-analysis. *Catheter Cardiovasc Interv* 2021; Epub ahead of print. PMID: 34779096. Full Text

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BACKGROUND: The optimal access site for cardiac catheterization in patients with prior coronary artery bypass surgery (CABG) continues to be debated. METHODS: We performed a random effects frequentist and Bayesian meta-analysis of 4 randomized trials and 18 observational studies, including 60,192 patients with prior CABG (27,236 in the radial group; 32,956 in the femoral group) that underwent cardiac catheterization. Outcomes included (1) access-site complications, (2) crossover to a different vascular access, (3) procedure time, and (4) contrast volume. Mean differences (MD) and 95% confidence interval (CI) were calculated for continuous outcomes and odds ratios (OR) and 95% CI for binary outcomes. RESULTS: Among randomized trials, crossover (OR: 7.63; 95% CI: 2.04, 28.51; p = 0.003) was higher in the radial group, while access site complications (OR: 0.96; 95% CI: 0.34, 2.87; p = 0.94) and contrast volume (MD: 15.08; 95% CI: -10.19, 40.35; p = 0.24) were similar. Among observational studies, crossover rates were higher (OR: 5.09; 95% CI: 2.43, 10.65; p < 0.001), while access site complication rates (OR: 0.52; 95% CI: 0.30, 0.89; p = 0.02) and contrast volume (MD: -7.52; 95% CI: -13.14, -1.90 ml; p = 0.009) were lower in the radial group. Bayesian analysis suggested that the odds of a difference existing between radial and femoral are small for all endpoints except crossover to another access site. CONCLUSION: In a frequentist and Bayesian meta-analysis of patients with prior CABG undergoing

coronary catheterization, radial access was associated with lower incidence of vascular access complications and lower contrast volume but also higher crossover rate.

Cardiology/Cardiovascular Research

Overstreet B, Kirkman D, **Qualters WK**, **Kerrigan D**, Haykowsky MJ, Tweet MS, Christle JW, **Brawner CA**, **Ehrman JK**, and **Keteyian SJ**. Rethinking Rehabilitation: A REVIEW OF PATIENT POPULATIONS WHO CAN BENEFIT FROM CARDIAC REHABILITATION. *J Cardiopulm Rehabil Prev* 2021; 41(6):389-399. PMID: 34727558. Full Text

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Although cardiac rehabilitation (CR) is safe and highly effective for individuals with various cardiovascular health conditions, to date there are only seven diagnoses or procedures identified by the Centers for Medicare & Medicaid Services that qualify for referral. When considering the growing number of individuals with cardiovascular disease (CVD), or other health conditions that increase the risk for CVD, it is important to determine the extent for which CR could benefit these populations. Furthermore, there are some patients who may currently be eligible for CR (spontaneous coronary artery dissection, left ventricular assistant device) but make up a relatively small proportion of the populations that are regularly attending and participating. Thus, these patient populations and special considerations for exercise might be less familiar to professionals who are supervising their programs. The purpose of this review is to summarize the current literature surrounding exercise testing and programming among four specific patient populations that either do not currently qualify for (chronic and end-stage renal disease, breast cancer survivor) or who are eligible but less commonly seen in CR (sudden coronary artery dissection, left ventricular assist device). While current evidence suggests that individuals with these health conditions can safely participate in and may benefit from supervised exercise programming, there is an immediate need for high-quality, multisite clinical trials to develop more specific exercise recommendations and support the inclusion of these populations in future CR programs.

Cardiology/Cardiovascular Research

Proudfoot AG, Kalakoutas A, Meade S, Griffiths MJD, **Basir M**, Burzotta F, Chih S, Fan E, Haft J, Ibrahim N, Kruit N, Lim HS, Morrow DA, Nakata J, Price S, Rosner C, Roswell R, Samaan MA, Samsky MD, Thiele H, Truesdell AG, van Diepen S, Voeltz MD, and Irving PM. Contemporary Management of Cardiogenic Shock: A RAND Appropriateness Panel Approach. *Circ Heart Fail* 2021; Epub ahead of print. PMID: 34807723. Full Text

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BACKGROUND: Current practice in cardiogenic shock is guided by expert opinion in guidelines and scientific statements from professional societies with limited high quality randomized trial data to inform optimal patient management. An international panel conducted a modified Delphi process with the intent of identifying aspects of cardiogenic shock care where there was uncertainty regarding optimal patient management. METHODS: An 18-person multidisciplinary panel comprising international experts was convened. A modified RAND/University of California Los Angeles appropriateness methodology was used. A survey comprising 70 statements was completed. Participants anonymously rated the appropriateness of each statement on a scale of 1 to 9: 1 to 3 inappropriate, 4 to 6 uncertain, and 7 to 9 appropriate. A summary of the results was discussed as a group, and the survey was iterated and completed again before final analysis. RESULTS: There was broad alignment with current international guidelines and consensus statements. Overall, 44 statements were rated as appropriate, 19 as uncertain, and 7 as inappropriate. There was no disagreement with a disagreement index <1 for all statements. Routine fluid administration was deemed to be inappropriate. Areas of uncertainty focused panel on pre-PCI interventions, the use of right heart catheterization to guide management, routine use of left ventricular unloading strategies, and markers of futility when considering escalation to mechanical circulatory support. CONCLUSIONS: While there was broad alignment with current guidance, an expert panel found several aspects of care where there was clinical equipoise, further highlighting the need for randomized controlled trials to better guide patient management and decision making in cardiogenic shock.

Cardiology/Cardiovascular Research

Sukul D, Seth M, Thompson MP, **Keteyian SJ**, Boyden TF, Syrjamaki JD, Yaser J, Likosky DS, and Gurm HS. Hospital and Operator Variation in Cardiac Rehabilitation Referral and Participation After Percutaneous Coronary Intervention: Insights From Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *Circ Cardiovasc Qual Outcomes* 2021; 14(11). PMID: 34749515. Full Text

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BACKGROUND: Despite its established benefit and strong endorsement in international guidelines, cardiac rehabilitation (CR) use remains low. Identifying determinants of CR referral and use may help develop targeted policies and quality improvement efforts. We evaluated the variation in CR referral and use across percutaneous coronary intervention (PCI) hospitals and operators. METHODS: We performed a retrospective observational cohort study of all patients who underwent PCI at 48 nonfederal Michigan hospitals between January 1, 2012 and March 31, 2018 and who had their PCI clinical registry record linked to administrative claims data. The primary outcomes included in-hospital CR referral and CR participation, defined as at least one outpatient CR visit within 90 days of discharge. Bayesian hierarchical regression models were fit to evaluate the association between PCI hospital and operator with CR referral and use after adjusting for patient characteristics. RESULTS: Among 54 217 patients who underwent PCI, 76.3% received an in-hospital referral for CR, and 27.1% attended CR within 90 days after discharge. There was significant hospital and operator level variation in in-hospital CR referral with median odds ratios of 3.88 (95% credible interval [CI], 3.06-5.42) and 1.64 (95% CI, 1.55-1.75), respectively, and in CR participation with median odds ratios of 1.83 (95% CI, 1.63-2.15) and 1.40 (95% CI, 1.35-1.47), respectively. In-hospital CR referral was significantly associated with an increased likelihood of CR participation (adjusted odds ratio, 1.75 [95% CI, 1.52-2.01]), and this association varied by treating PCI hospital (odds ratio range, 0.92-3.75) and operator (odds ratio range, 1.26-2.82). CONCLUSIONS: In-hospital CR referral and 90-day CR use after PCI varied significantly by hospital and operator. The association of in-hospital CR referral with downstream CR use also varied across hospitals and less so across operators suggesting that specific hospitals and operators may more effectively translate CR referrals into downstream use. Understanding the factors that explain this variation will be critical to developing strategies to improve CR participation overall.

Cardiology/Cardiovascular Research

Torpoco Rivera DM, **Williams CT**, and Karpawich PP. Cardiac Amyloidosis in a Child Presenting with Syncope: The First Reported Case and a Diagnostic Dilemma. *Pediatr Cardiol* 2021; Epub ahead of print. PMID: 34783874. Full Text

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Cardiac amyloidosis is a rare cause of cardiomyopathy, reported exclusively in adults. We report the first known case presenting in childhood. A 12-year-old boy presented with syncope and diagnosed with ventricular non-compaction by echocardiography. Eventual genetic testing confirmed a TTR gene mutation associated with hereditary transthyretin amyloidosis.

Cardiology/Cardiovascular Research

Villablanca PA, Vemulapalli S, Stebbins A, Dai D, **So CY**, **Eng MH**, **Wang DD**, **Frisoli TM**, **Lee JC**, **Kang G**, Szerlip M, Ibrahim H, Staniloae C, Gaba P, **Lemor A**, Finn M, Ramakrishna H, Williams MR, Leon MB, **O'Neill WW**, and Shah B. Sex-Based Differences in Outcomes With Percutaneous Transcatheter Repair of Mitral Regurgitation With the MitraClip System: Transcatheter Valve Therapy Registry From 2011 to 2017. *Circ Cardiovasc Interv* 2021; 14(11). PMID: 34784236. Full Text

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BACKGROUND: Women have a higher rate of adverse events after mitral valve surgery. We sought to evaluate whether outcomes after transcatheter edge-to-edge repair intervention by sex have similar trends to mitral valve surgery. METHODS: The primary outcome was 1-year major adverse events defined as a composite of all-cause mortality, stroke, and any bleeding in the overall study cohort. Patients who underwent transcatheter edge-to-edge repair for mitral regurgitation with the MitraClip system in the Society of Thoracic Surgery/American College of Cardiology Transcatheter Valve Therapy registry were evaluated. Linked administrative claims from the Centers for Medicare and Medicaid Services were used to evaluate 1-year clinical outcomes. Associations between sex and outcomes were evaluated using a multivariable logistic regression model for in-hospital outcomes and Cox model for 1-year outcomes. RESULTS: From November 2013 to March 2017, 5295 patients, 47.6% (n=2523) of whom were female, underwent transcatheter edge-to-edge repair. Females were less likely to have >1 clip implanted (P<0.001) and had a lower adjusted odds ratio of device success (adjusted odds ratio, 0.78 [95% CI, 0.67-0.90]), driven by lower odds of residual mitral gradient <5 mm Hg (adjusted odds ratio, 0.54 [CI, 0.46-0.63]) when compared with males. At 1-year follow-up, the primary outcome did not differ by sex. Female sex was associated with lower adjusted 1-year risk of all-cause mortality (adjusted hazard ratio, 0.80 [CI, 0.68-0.94]), but the adjusted 1-year risk of stroke and any bleeding did not differ by sex. CONCLUSIONS: No difference in composite outcome of all-cause mortality, stroke, and any bleeding was observed between females and males. Adjusted 1-year all-cause mortality was lower in females compared with males.

Cardiology/Cardiovascular Research

Wang DD, **O'Neill BP**, Caranasos TG, Chitwood WR, Jr., Stack RS, and **O'Neill WW**. Comparative differences of mitral valve-in-valve implantation: A new mitral bioprosthesis versus current mosaic and epic valves. *Catheter Cardiovasc Interv* 2021; Epub ahead of print. PMID: 34843639. Full Text

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OBJECTIVE: Evaluate transcatheter mitral valve replacement (TMVR) valve-in-valve (VIV) outcomes in three different mitral bioprostheses (of comparable measured internal diameters) under stable hemodynamic and surgical conditions by bench, echocardiographic, computerized tomography (CT), and autopsy comparisons pre- and post-valve implantation in a porcine model under matched controlled conditions. BACKGROUND: Impact of surgical bioprosthesis design on TMVR VIV procedures is unknown. METHODS: Fifteen similar-sized Yorkshire pigs underwent pre-procedural CT screening. Twelve had consistent anatomic features and underwent implantation of mitral bioprostheses. Four valves from each of three manufacturers were implanted in randomized fashion: 27-mm Epic, 27-mm Mosaic, and 25-mm Mitris, followed by TMVR VIV with 26 Edwards Sapien3. Post-VIV, suprasternal TEE studies were performed to assess hemodynamic function, followed by a gated contrast CT. After euthanasia, animals underwent necropsy for anatomic evaluation. RESULTS: All 12 animals had successful VIV implantation with no study deaths. The post vivMitris (3.77 ± 0.36)/(2.2 ± 0.25 mmHg) had the lowest peak/mean trans-mitral gradient and the vivEpic the highest (15.5 ± 2.55)/(7.09 ± 1.13 mmHg). All THVs (transcatheter heart valves) had greatest deformation within the center of the THV frame; with the smallest waist opening area in the vivEpic (329 ± 35.8 mm(2)) and greatest in the vivMitris (414 ± 33.12 mm(2)). Bioprosthetic frames without obvious radiopaque markers resulted in the most

ventricular implantation of the THV's anteroseptal frame (Epic: -4.52 ± 0.76 mm), versus the most radiopaque bioprosthesis (Mitris: -1.18 ± 2.95 mm), and higher peak LVOT gradients (Epic: 4.82 ± 1.61 mmHg; Mitris: 2.91 ± 1.47 mmHg). CONCLUSIONS: The current study demonstrates marked variations in hemodynamics, THV opening area, and anatomic dimensions among measured similarly sized mitral bioprostheses. These data suggest a critical need for understanding the potential impact of variations in bioprosthesis design on TMVR VIV clinical outcomes.

Center for Health Policy and Health Services Research

Doll KM, Howard AG, Stürmer T, Carey T, Nicholson WK, Carey E, Myers E, **Nerenz D**, and Robinson WR. Development of an algorithm to assess unmeasured symptom severity in gynecologic care. *Am J Obstet Gynecol* 2021; Epub ahead of print. PMID: 34752734. Full Text

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BACKGROUND: Healthcare disparities research is often limited by incomplete accounting for differences in health status by populations. In the United States, hysterectomy shows marked variation by race and geography, but it is difficult to understand what factors cause these variations without accounting for differences in the severity of gynecologic symptoms that drive the decision-making for hysterectomy. OBJECTIVE: This study aimed to demonstrate a method for using electronic health record-derived data to create composite symptom severity indices to more fully capture relevant markers that influence the decision for hysterectomy. STUDY DESIGN: This was a retrospective cohort study of 1993 women who underwent hysterectomy between April 4, 2014, and December 31, 2017, from 10 hospitals and >100 outpatient clinics in North Carolina. Electronic health record data, including billing, pharmacy, laboratory data, and free-text notes, were used to identify markers of 3 common indications for hysterectomy: bulk symptoms (pressure from uterine enlargement), vaginal bleeding, and pelvic pain. To develop weighted symptom indices, we finalized a scoring algorithm based on the relationship of each marker to an objective measure, in combination with clinical expertise, with the goal of composite symptom severity indices that had sufficient variation to be useful in comparing different patient groups and allow discrimination among severe symptoms of bulk, bleeding, or pain. RESULTS: The ranges of symptom severity scores varied across the 3 indices, including composite bulk score (0-14), vaginal bleeding score (0-44), and pain score (0-30). The mean values of each composite symptom severity index were greater for those who had diagnostic codes for vaginal bleeding, bulk symptoms, or pelvic pain, respectively. However, each index demonstrated a variation across the entire group of hysterectomy cases and identified symptoms that ranged in severity among those with and without the target diagnostic codes. CONCLUSION: Leveraging multisource data to create composite symptom severity indices provided

greater discriminatory power to assess common gynecologic indications for hysterectomy. These methods can improve the understanding in healthcare use in the setting of long-standing inequities and be applied across populations to account for previously unexplained variations across race, geography, and other social indicators.

Center for Health Policy and Health Services Research
Goger P, Zerr AA, Weersing VR, Dickerson JF, Crawford PM, Sterling SA, Waitzfelder B, Daida YG, **Ahmedani BK**, Penfold RB, and Lynch FL. Health Service Utilization Among Children and Adolescents with Posttraumatic Stress Disorder: A Case-Control Study. *J Dev Behav Pediatr* 2021; Epub ahead of print. PMID: 34817448. Full Text

SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA; California State University Channel Islands, Camarillo, CA; Kaiser Permanente Center for Health Research, Portland, OR; Kaiser Permanente Division of Research, Oakland, CA; Kaiser Permanente Center for Integrated Health Care Research, Honolulu, HI; Center for Health Services Research, Henry Ford Health System, Detroit, MI; Kaiser Permanente Washington Health Research Institute, Seattle, WA.

OBJECTIVE: Trauma exposure is widely prevalent, with more than 60% of adolescents having experienced at least 1 traumatic event and a third of those at high risk to develop posttraumatic stress disorder (PTSD). Data are scarce and out of date on the services children and adolescents with PTSD receive, impeding efforts to improve care and outcomes. This study examines health service use for a large and diverse sample of children and adolescents with and without a diagnosis of PTSD. METHOD: Using a matched case-control study, we gathered information from 4 large health care systems participating in the Mental Health Research Network. Data from each site's electronic medical records on diagnoses, health care encounters, and demographics were analyzed. Nine hundred fifty-five 4- to 18-year-olds with a diagnosis of PTSD were identified and matched on a 1:5 ratio to 4770 controls. We compared cases with controls on frequency of service use in outpatient primary care, medical specialty care, acute care, and mental health care. We also assessed psychotropic medication use. RESULTS: Children and adolescents diagnosed with PTSD used nearly all physical and mental health service categories at a higher rate than controls. However, one-third of children and adolescents did not receive even 1 outpatient mental health visit (36.86%) during the year-long sampling window. CONCLUSION: Our findings suggest that children and adolescents diagnosed with PTSD may have unmet mental health needs. They are high utilizers of health services overall, but lower utilizers of the sectors that may be most helpful in resolving their symptoms.

Center for Health Policy and Health Services Research
Scheuer H, Kuklinski MR, Sterling SA, Catalano RF, Beck A, **Braciszewski J**, Boggs J, Hawkins JD, **Loree AM**, Weisner C, Carey S, **Elsiss F**, Morse E, Negusse R, Jessen A, Kline-Simon A, Oesterle S, Quesenberry C, Sofrygin O, and **Yoon T**. Parent-focused prevention of adolescent health risk behavior: Study protocol for a multisite cluster-randomized trial implemented in pediatric primary care. *Contemp Clin Trials* 2021; 112:106621. PMID: 34785305. Full Text

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Evidence-based parenting interventions play a crucial role in the sustained reduction of adolescent behavioral health concerns. Guiding Good Choices (GGC) is a 5-session universal anticipatory guidance curriculum for parents of early adolescents that has been shown to reduce substance use, depression symptoms, and delinquent behavior. Although prior research has demonstrated the effectiveness of evidence-based parenting interventions at achieving sustained reductions in adolescent behavioral health concerns, public health impact has been limited by low rates of uptake in community and agency settings. Pediatric primary care is an ideal setting for implementing and scaling parent-focused prevention programs as these settings have a broad reach, and prevention programs implemented within them have the potential to achieve population-level impact. The current investigation, Guiding Good Choices for Health (GGC4H), tests the feasibility and effectiveness of implementing GGC in 3 geographically and socioeconomically diverse large integrated healthcare systems. This pragmatic, cluster randomized clinical trial will compare GGC parenting intervention to usual pediatric primary care practice, and will include approximately 3750 adolescents; n = 1875 GGC intervention and n = 1875 usual care. The study team hypothesizes that adolescents whose parents are randomized into the GGC intervention arm will show reductions in substance use initiation, the study's primary outcomes, and other secondary (e.g., depression symptoms, substance use prevalence) and exploratory outcomes (e.g., health services utilization, anxiety symptoms). The investigative team anticipates that the implementation of GGC within pediatric primary care clinics will successfully fill an unmet need for effective preventive parenting interventions. Trial registration: Clinicaltrials.govNCT04040153.

Dermatology

Alavi A, Baradaran S, Mathias SD, Colwell HH, Song M, **Hamzavi IH**, and Han C. Development of a Patient-Reported Outcome Questionnaire to Assess Signs and Symptoms of Hidradenitis Suppurativa: The Hidradenitis Suppurativa Symptom Diary (HSSD). *J Am Acad Dermatol* 2021; Epub ahead of print. PMID: 34808326. Full Text

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Dermatology

Callender VD, Baldwin H, Cook-Bolden FE, Alexis AF, **Stein Gold L**, and Guenin E. Effects of Topical Retinoids on Acne and Post-inflammatory Hyperpigmentation in Patients with Skin of Color: A Clinical Review and Implications for Practice. *Am J Clin Dermatol* 2021; Epub ahead of print. PMID: 34751927. Full Text

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Acne is a common cause for post-inflammatory hyperpigmentation (PIH), particularly in patients with skin of color (SOC), and PIH is often more distressing to patients than the acne itself. Topical retinoids are approved for the treatment of acne and for pigmentation disorders such as melasma or mottled hyperpigmentation associated with photodamage; moreover, they have been shown to reduce hyperpigmentation in patients with SOC. Therefore, treatment with topical retinoids should be started as early as possible unless contraindicated. Use of novel formulations or application of commonly recommended moisturizers may help reduce irritation. Combining retinoids with other topical agents and procedures such as superficial chemical peels can help to improve hyperpigmentation. Primary acne lesions are likely to improve weeks before PIH resolves and helping patients manage their expectations may reduce frustration. Providing clinicians and researchers with more education about the presentation and management of dermatologic conditions in patients with SOC is also recommended.

Dermatology

Enescu CD, **Patel A**, and **Friedman BJ**. Unique Recognizable Histopathologic Variant of Palisaded Neutrophilic and Granulomatous Dermatitis that Is Associated With SRSF2-Mutated Chronic Myelomonocytic Leukemia: Case Report and Review of the Literature. *Am J Dermatopathol* 2021; Epub ahead of print. PMID: 34783709. Full Text

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Palisaded neutrophilic and granulomatous dermatitis (PNGD) represents a cutaneous histopathologic reaction spectrum associated with several underlying disorders. Few cases of PNGD have been associated with chronic myelomonocytic leukemia (CMML), a malignant hematopoietic disorder with features in between those of a myeloproliferative neoplasm and myelodysplastic syndrome. We present a patient with a generalized papular skin reaction involving the neck, chest, and shoulders with histomorphological features on the spectrum of PNGD. Subsequent laboratory workup demonstrated a persistent mild monocytosis, raising concern for CMML. The diagnosis was ultimately confirmed with a bone marrow biopsy and associated mutational analysis through next-generation sequencing which identified deleterious variants in SRSF2, IDH2, and ASXL1. The findings in this case strengthen the previously made association between PNGD and SRSF2-mutated CMML and may help better define a unique recognizable clinical-histopathological-molecular subtype for dermatopathologists.

Dermatology

Jahnke MN, O'Haver J, Gupta D, Hawryluk EB, Finelt N, Kruse L, Jen M, Horii KA, Frieden IJ, Price H, and Coughlin CC. Care of Congenital Melanocytic Nevi in Newborns and Infants: Review and Management Recommendations. *Pediatrics* 2021; Epub ahead of print. PMID: 34845496. Full Text

Department of Dermatology, Henry Ford Health System, Detroit, Michigan.
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A pediatric dermatology expert working group performed a narrative review to describe care related to congenital melanocytic nevi (CMN) in neonates and infants. There are no published guidelines for most aspects of care, including routine skin care and visit intervals. Few guidelines exist for surgical management; newer recommendations favor conservative practice. Emerging evidence contributes to recommendations for screening MRI to evaluate for neural melanosis and related central nervous system complications, however, more research is needed. Risk for melanoma is generally low, but those with large, giant, or multiple CMN have a higher risk. Multidisciplinary care, with a focus on family and patient preferences, is of paramount importance. Without standardized screening and management guidelines, questions abound regarding appropriate physical examination intervals, potential treatment including full or partial excision, timing and frequency of imaging, melanoma risk, and assessment for neural melanosis. This review highlights the current state of knowledge concerning care of patients with CMN, reveals gaps in the literature surrounding skin care, and provides management recommendations. We additionally discuss cutaneous complications of CMN, such as pruritus, hypertrichosis, and wound healing. Resources and references for families and providers can help patients navigate this sometimes challenging diagnosis. Finally, we contribute expert care recommendations to the current body of literature as a foundation for the development of future, more comprehensive care guidelines.

Dermatology

Maghfour J, **Boothby-Shoemaker W**, and **Lim HW**. Evaluating the United States Population's Interest in Sunscreen: A Google Trend Analysis. *Clin Exp Dermatol* 2021; Epub ahead of print. PMID: 34798683. Full Text

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Broad-spectrum sunscreen remains an important component of photoprotection against deleterious effects of ultraviolet (UV) radiation.(1) The advances made in the field of photoprotection has resulted in an expansion of various sunscreen formulations, providing numerous options to consumers. In the past several years, there has been a growing concern regarding the potential environmental and health impacts of certain UVR filters, which has resulted in public confusion on the use of sunscreen as a photoprotective measure.(1,2).

Dermatology
Osto M, **Hamzavi IH**, **Lim HW**, and **Kohli I**. Individual Typology Angle and Fitzpatrick Skin Phototypes are Not Equivalent in Photodermatology. *Photochem Photobiol* 2021; Epub ahead of print. PMID: 34796498. Full Text

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Individual typology angle (ITA) measures constitutive pigmentation while skin phototypes (SPT) categories are based on sun reactiveness. However, the association between the two, ITA and SPT, is yet to be established. Since both systems provide six categories, recent studies have used ITA classifications as synonymous to SPT. The results of this study indicate that these cannot be utilized interchangeably. In conclusion, poor correlation between the six objective individual typology angle categories and the subjective Fitzpatrick skin phototype categories was established along with highlighting ITAs potential in photobiologic studies and objective standardization of skin type classifications.

Dermatology
Parashar K, **Torres AE**, **Boothby-Shoemaker W**, **Kohli I**, **Veenstra J**, Neel V, and **Ozog DM**. Imaging Technologies for Pre-surgical Margin Assessment of Basal Cell Carcinoma. *J Am Acad Dermatol* 2021; Epub ahead of print. PMID: 34793927. Full Text

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Basal cell carcinoma is the most common cancer worldwide, necessitating the development of techniques to decrease treatment costs through efficiency and efficacy. Mohs micrographic surgery, a specialized surgical technique involving staged resection of the tumor with complete histologic evaluation of the peripheral margins, is highly utilized. Reducing stages by even 5-10% would result in significant improvement in care and economic benefits. Non-invasive imaging could aid in both establishing the diagnosis of suspicious skin lesions and streamlining the surgical management of skin cancers by improving pre-surgical estimates of tumor size. Herein, we review the current state of imaging techniques in dermatology and their application for diagnosis and tumor margin assessment of basal cell carcinoma prior to Mohs micrographic surgery.

Dermatology
Tisack A, Luther C, and **Kohen L**. Linear Violaceous Papules in a Child. *Cutis* 2021; 108(5):241-245. PMID: Not assigned. Full Text

Diagnostic Radiology
Mousavi Mojab SZ, **Shams S**, Fotouhi F, and **Soltanian-Zadeh H**. EpistoNet: an ensemble of Epistocracy-optimized mixture of experts for detecting COVID-19 on chest X-ray images. *Sci Rep* 2021; 11(1):21564. PMID: 34732741. Full Text

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The Coronavirus has spread across the world and infected millions of people, causing devastating damage to the public health and global economies. To mitigate the impact of the coronavirus a reliable, fast, and accurate diagnostic system should be promptly implemented. In this study, we propose EpistoNet, a decision tree-based ensemble model using two mixtures of discriminative experts to classify COVID-19 lung infection from chest X-ray images. To optimize the architecture and hyper-parameters of the designed neural networks, we employed Epistocracy algorithm, a recently proposed hyper-heuristic evolutionary method. Using 2500 chest X-ray images consisting of 1250 COVID-19 and 1250 non-COVID-19 cases, we left out 500 images for testing and partitioned the remaining 2000 images into 5 different clusters using K-means clustering algorithm. We trained multiple deep convolutional neural networks on each cluster to help build a mixture of strong discriminative experts from the top-performing models supervised by a gating network. The final ensemble model obtained 95% accuracy on COVID-19 images and 93% accuracy on non-COVID-19. The experimental results show that EpistoNet can accurately, and reliably be used to detect COVID-19 infection in the chest X-ray images, and Epistocracy algorithm can be effectively used to optimize the hyper-parameters of the proposed models.

Diagnostic Radiology
Silosky M, Marsh R, and **Bevins NB**. Features to Consider When Selecting Displays for Remote Reading. *J Am Coll Radiol* 2021; Epub ahead of print. PMID: 34780775. Full Text

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Diagnostic Radiology
Smith-Bindman R, Yu S, Wang Y, Kohli MD, Chu P, Chung R, Luong J, Bos D, Stewart C, Bista B, Alejandrez Cisneros A, Delman B, Einstein AJ, **Flynn M**, Romano P, Seibert JA, Westphalen AC, and Bindman A. An Image Quality-informed Framework for CT Characterization. *Radiology* 2021; Epub ahead of print.:210591. PMID: 34751618. Full Text

From the Department of Radiology and Biomedical Imaging (R.S.B., S.Y., Y.W., M.D.K., P.C., R.C., J.L., C.S.), Department of Epidemiology and Biostatistics (R.S.B., A.B.), Philip R. Lee Institute for Health Policy Studies (R.S.B., A.B.), and Department of Medicine (A.B.), University of California San Francisco (UCSF), UCSF Mission Bay Campus, Mission Hall: Global Health and Clinical Sciences Building, 550 16th St, 2nd Floor, Box 0560, San Francisco, CA 94158; Department of Demography, University of California Berkeley, Berkeley, Calif (R.C.); Institute of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Essen, Germany (D.B.); Department of Radiology and Biomedical Imaging, University of California Irvine, Irvine, Calif (B.B.); UCSF Medical School, San Francisco, Calif (A.A.C.); Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY (B.D.); Seymour, Paul, and Gloria Milstein Division of Cardiology, Department of Medicine, and Department of Radiology, Columbia University Irving Medical Center and New York-Presbyterian Hospital, New York, NY (A.J.E.); Department of Radiology and Public Health Sciences, Henry Ford Health System, Detroit, Mich (M.F.); Department of Nuclear Engineering and Radiological Science, University of Michigan, Ann Arbor, Mich (M.F.); Department of Medicine and Pediatrics (P.R.) and Department of Radiology (J.A.S.), University of California Davis Health, Sacramento, Calif; and Department of Radiology, University of Washington, Seattle, WA (A.C.W.).

Background Lack of standardization in CT protocol choice contributes to radiation dose variation. Purpose To create a framework to assess radiation doses within broad CT categories defined according to body region and clinical imaging indication and to cluster indications according to the dose required for sufficient image quality. Materials and Methods This was a retrospective study using Digital Imaging and Communications in Medicine metadata. CT examinations in adults from January 1, 2016 to December 31, 2019 from the University of California San Francisco International CT Dose Registry were grouped into 19 categories according to body region and required radiation dose levels. Five body regions had a single

dose range (ie, extremities, neck, thoracolumbar spine, combined chest and abdomen, and combined thoracolumbar spine). Five additional regions were subdivided according to dose. Head, chest, cardiac, and abdomen each had low, routine, and high dose categories; combined head and neck had routine and high dose categories. For each category, the median and 75th percentile (ie, diagnostic reference level [DRL]) were determined for dose-length product, and the variation in dose within categories versus across categories was calculated and compared using an analysis of variance. Relative median and DRL (95% CI) doses comparing high dose versus low dose categories were calculated. Results Among 4.5 million examinations, the median and DRL doses varied approximately 10 times between categories compared with between indications within categories. For head, chest, abdomen, and cardiac (3 266 546 examinations [72%]), the relative median doses were higher in examinations assigned to the high dose categories than in examinations assigned to the low dose categories, suggesting the assignment of indications to the broad categories is valid (head, 3.4-fold higher [95% CI: 3.4, 3.5]; chest, 9.6 [95% CI: 9.3, 10.0]; abdomen, 2.4 [95% CI: 2.4, 2.5]; and cardiac, 18.1 [95% CI: 17.7, 18.6]). Results were similar for DRL doses (all P < .001). Conclusion Broad categories based on image quality requirements are a suitable framework for simplifying radiation dose assessment, according to expected variation between and within categories. © RSNA, 2021 See also the editorial by Mahesh in this issue.

Emergency Medicine

Baca JT, Parchim NF, Kotulski J, Femling J, Taylor RM, Bussmann S, Candelaria L, Norii T, **Moyer M**, **Laliberte R**, **Patel S**, **Odeesho S**, and **Nowak R**. Feasibility and Initial Safety Evaluation of Inhaled (13)C-Urea in Ambulatory Patients with Pneumonia. *J Aerosol Med Pulm Drug Deliv* 2021; Epub ahead of print. PMID: 34748404. Full Text

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Emergency Medicine

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BACKGROUND: The 2020 European Society of Cardiology (ESC) guidelines recommend using the 0/1-hour and 0/2-hour algorithms over the 0/3-hour algorithm as the first and second choices of high-sensitivity cardiac troponin (hs-cTn)-based strategies for triage of patients with suspected acute myocardial infarction (AMI). PURPOSE: To evaluate the diagnostic accuracies of the ESC 0/1-hour, 0/2-hour, and 0/3-hour algorithms. DATA SOURCES: PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus from 1 January 2011 to 31 December 2020. (PROSPERO: CRD42020216479). STUDY SELECTION: Prospective studies that evaluated the ESC 0/1-hour, 0/2-hour, or 0/3-hour algorithms in adult patients presenting with suspected AMI. DATA EXTRACTION: The primary outcome was index AMI. Twenty unique cohorts were identified. Primary data were obtained from investigators of 16 cohorts and aggregate data were extracted from 4 cohorts. Two independent authors assessed each study for methodological quality. DATA SYNTHESIS: A total of 32 studies (20 cohorts) with 30 066 patients were analyzed. The 0/1-hour algorithm had a pooled sensitivity of 99.1% (95% CI, 98.5% to 99.5%) and negative predictive value (NPV) of 99.8% (CI, 99.6% to 99.9%) for ruling out AMI. The 0/2-hour algorithm had a pooled sensitivity of 98.6% (CI, 97.2% to 99.3%) and NPV of 99.6% (CI, 99.4% to 99.8%). The 0/3-hour algorithm had a pooled sensitivity of 93.7% (CI, 87.4% to 97.0%) and NPV of 98.7% (CI, 97.7% to 99.3%). Sensitivity of the 0/3-hour algorithm was attenuated in studies that did not use clinical criteria (GRACE score <140 and pain-free) compared with studies that used clinical criteria (90.2% [CI, 82.9 to 94.6] vs. 98.4% [CI, 88.6 to 99.8]). All 3 algorithms had similar specificities and positive predictive values for ruling in AMI, but heterogeneity across studies was substantial. Diagnostic performance was similar across the hs-cTnT (Elecsys; Roche), hs-cTnI (Architect; Abbott), and hs-cTnI (Centaur/Atellica; Siemens) assays. LIMITATION: Diagnostic accuracy, inclusion and exclusion criteria, and cardiac troponin sampling time varied among studies. CONCLUSION: The ESC 0/1-hour and 0/2-hour algorithms have higher sensitivities and NPVs than the 0/3-hour algorithm for index AMI. PRIMARY FUNDING SOURCE: National Taiwan University Hospital.

Emergency Medicine

Correa K, Craver S, and **Sandhu A**. An Uncommon Presentation of Cryptococcal Meningitis in an Immunocompetent Patient: A Case Report. *Clin Pract Cases Emerg Med* 2021; 5(4):450-454. PMID: 34813442. Full Text

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INTRODUCTION: Meningitis is a serious and potentially life-threatening infection of the central nervous system. Cryptococcus neoformans is a rare fungal cause of meningitis that commonly presents with atypical symptoms. Although this infection is most common in immunocompromised patients, it also occurs in immunocompetent patients. This case report describes an atypical presentation of cryptococcal

meningitis in a seemingly immunocompetent patient. CASE REPORT: A 40-year-old immunocompetent patient with no significant past medical history had visited the emergency department (ED) five times within a span of 30 days reporting dental pain and headache. Throughout each of the visits, no clear symptoms signaling the need for a meningitis workup were observed, as the patient had been afebrile, displayed no nuchal rigidity, and his presenting symptoms subsided within the ED after treatment. A lumbar puncture was performed after emergency medical services brought the patient in for his sixth ED visit, initially for stroke-like symptoms and altered mental status. Spinal fluid was indicative of cryptococcal meningitis. CONCLUSION: This case highlights the challenge of identifying cryptococcal meningitis in the ED, particularly in immunocompetent patients who do not display classic meningitis symptoms. It also highlights the importance of keeping a broad differential and carefully ruling out diagnoses when patients return to the ED multiple times for the same complaint.

Emergency Medicine

Germine LT, Joormann J, Passell E, Rutter LA, Scheuer L, Martini P, Hwang I, Lee S, Sampson N, Barch DM, House SL, Beaudoin FL, An X, Stevens JS, Zeng D, Linnstaedt SD, Jovanovic T, Clifford GD, Neylan TC, Rauch SL, **Lewandowski C**, Hendry PL, Sheikh S, Storrow AB, Musey PI, Jr., Jones CW, Punches BE, McGrath ME, Pascual JL, Mohiuddin K, Pearson C, Peak DA, Domeier RM, Bruce SE, Rathlev NK, Sanchez LD, Pietrzak RH, Pizzagalli DA, Harte SE, Elliott JM, Koenen KC, Ressler KJ, McLean SA, and Kessler RC. Neurocognition after motor vehicle collision and adverse post-traumatic neuropsychiatric sequelae within 8 weeks: Initial findings from the AURORA study. *J Affect Disord* 2021; Epub ahead of print. PMID: 34800569. Full Text

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BACKGROUND: Previous work has indicated that differences in neurocognitive functioning may predict the development of adverse post-traumatic neuropsychiatric sequelae (APNS). Such differences may be vulnerability factors or simply correlates of APNS-related symptoms. Longitudinal studies that measure neurocognitive functioning at the time of trauma are needed to determine whether such differences precede the development of APNS. METHODS: Here, we present findings from a subsample of 666 ambulatory patients from the AURORA (Advancing Understanding of RecOvery afteR traumA) study. All patients presented to EDs after a motor vehicle collision (MVC). We examined associations of neurocognitive test performance shortly after MVC with peritraumatic symptoms in the ED and APNS (depression, post-traumatic stress, post-concussive symptoms, and pain) 2 weeks and 8 weeks later. Neurocognitive tests assessed processing speed, attention, verbal reasoning, memory, and social perception. RESULTS: Distress in the ED was associated with poorer processing speed and short-term memory. Poorer short-term memory was also associated with depression at 2 weeks post-MVC, even after controlling for peritraumatic distress. Finally, higher vocabulary scores were associated with pain 2 weeks post-MVC. LIMITATIONS: Self-selection biases among those who present to the ED and enroll in the study limit generalizability. Also, it is not clear whether observed neurocognitive differences predate MVC exposure or arise in the immediate aftermath of MVC exposure. CONCLUSIONS: Our results suggest that processing speed and short-term memory may be useful predictors of trauma-related characteristics and the development of some APNS, making such measures clinically-relevant for identifying at-risk individuals.

Emergency Medicine

Johnson AM, **Cunningham CJ**, Arnold E, Rosamond WD, and Zègre-Hemsey JK. Impact of Using Drones in Emergency Medicine: What Does the Future Hold? *Open Access Emerg Med* 2021; 13:487-498. PMID: 34815722. Full Text

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The use of unmanned aerial vehicles or "drones" has expanded in the last decade, as their technology has become more sophisticated, and costs have decreased. They are now used routinely in farming, environmental surveillance, public safety, commercial product delivery, recreation, and other applications. Health-related applications are only recently becoming more widely explored and accepted. The use of drone technology in emergency medicine is especially promising given the need for a rapid response to enhance patient outcomes. The purpose of this paper is to describe some of the main current and expanding applications of drone technology in emergency medicine and to describe challenges and future opportunities. Current applications being studied include delivery of defibrillators in response to out-of-hospital cardiac arrest, blood and blood products in response to trauma, and rescue medications. Drones are also being studied and actively used in emergency response to search and rescue operations as well as disaster and mass casualty events. Current challenges to expanding their use in emergency medicine and emergency medical system (EMS) include regulation, safety, flying conditions, concerns about privacy, consent, and confidentiality, and details surrounding the development, operation, and maintenance of a medical drone network. Future research is needed to better understand end user perceptions and acceptance. Continued technical advances are needed to increase payload capacities, increase flying distances, and integrate drone networks into existing 9-1-1 and EMS systems. Drones are a promising technology for improving patient survival, outcomes, and quality of life, particularly for those in areas that are remote or that lack funds or infrastructure. Their cost savings compared with ground transportation alone, speed, and convenience make them particularly applicable in the field of emergency medicine. Research to date suggests that use of drones in emergency medicine is feasible, will be accepted by the public, is cost-effective, and has broad application.

Emergency Medicine

Liangou A, Tasoglou A, Huber HJ, Wistrom C, **Brody K**, Menon PG, **Bebekoski T**, **Menschel K**, **Davidson-Fiedler M**, DeMarco K, Salphale H, Wistrom J, Wistrom S, and Lee RJ. A method for the identification of COVID-19 biomarkers in human breath using Proton Transfer Reaction Time-of-Flight Mass Spectrometry. *EClinicalMedicine* 2021; 42:101207. PMID: 34841237. Full Text

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BACKGROUND: COVID-19 has caused a worldwide pandemic, making the early detection of the virus crucial. We present an approach for the determination of COVID-19 infection based on breath analysis. METHODS: A high sensitivity mass spectrometer was combined with artificial intelligence and used to develop a method for the identification of COVID-19 in human breath within seconds. A set of 1137 positive and negative subjects from different age groups, collected in two periods from two hospitals in the USA, from 26 August, 2020 until 15 September, 2020 and from 11 September, 2020 until 11 November, 2020, was used for the method development. The subjects exhaled in a Tedlar bag, and the exhaled breath samples were subsequently analyzed using a Proton Transfer Reaction Time-of-Flight Mass Spectrometer (PTR-ToF-MS). The produced mass spectra were introduced to a series of machine

learning models. 70% of the data was used for these sub-models' training and 30% was used for testing. FINDINGS: A set of 340 samples, 95 positives and 245 negatives, was used for the testing. The combined models successfully predicted 77 out of the 95 samples as positives and 199 out of the 245 samples as negatives. The overall accuracy of the model was 81.2%. Since over 50% of the total positive samples belonged to the age group of over 55 years old, the performance of the model in this category was also separately evaluated on 339 subjects (170 negative and 169 positive). The model correctly identified 166 out of the 170 negatives and 164 out of the 169 positives. The model accuracy in this case was 97.3%. INTERPRETATION: The results showed that this method for the identification of COVID-19 infection is a promising tool, which can give fast and accurate results.

Emergency Medicine

Michaelis T, **Gunaga S**, **McKechnie T**, and **Shafiq Q**. Acute Myocardial Infarction in a Patient with Twin Pregnancy: A Case Report. *Clin Pract Cases Emerg Med* 2021; 5(4):507-510. PMID: 34813459. Full Text

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INTRODUCTION: Acute myocardial infarction (AMI) rarely occurs during pregnancy and presents unique challenges in diagnosis and management. Traditionally, pregnancy has not readily been considered a risk factor for AMI in the emergency department despite the potential for adverse impacts on maternal and fetal health. As cardiovascular risk factors and advanced maternal age become more prevalent in society over time, the incidence will continue to increase. Prior cases with singular gestation have been reported; however, only one previous case during a twin pregnancy was identified in the medical literature. CASE REPORT: We describe a rare case of acute ST-segment elevation myocardial infarction in a 37-year-old woman at 24 weeks gestation with a dichorionic diamniotic twin pregnancy. CONCLUSION: It is important for the emergency physician to recognize acute coronary syndrome as a part of the differential diagnosis of chest pain in pregnant patients and be familiar with the diagnostic and management options available for this special population.

Emergency Medicine

Seligowski AV, Steuber ER, Hinrichs R, Reda MH, Wiltshire CN, Wanna CP, Winters SJ, Phillips KA, House SL, Beaudoin FL, An X, Stevens JS, Zeng D, Neylan TC, Clifford GD, Linnstaedt SD, Germine LT, Bollen KA, Guffanti G, Rauch SL, Haran JP, Storrow AB, **Lewandowski C**, Musey PI, Jr., Hendry PL, Sheikh S, Jones CW, Punches BE, Kurz MC, Murty VP, McGrath ME, Hudak LA, Pascual JL, Seamon MJ, Datner EM, Chang AM, Pearson C, Peak DA, Merchant RC, Domeier RM, Rathlev NK, O'Neil BJ, Sanchez LD, Bruce SE, Miller MW, Pietrzak RH, Joormann J, Barch DM, Pizzagalli DA, Sheridan JF, Luna B, Harte SE, Elliott JM, Koenen KC, Kessler RC, McLean SA, Ressler KJ, and Jovanovic T. A prospective examination of sex differences in posttraumatic autonomic functioning. *Neurobiol Stress* 2021; 15:100384. PMID: 34485632. Full Text

BACKGROUND: Cross-sectional studies have found that individuals with posttraumatic stress disorder (PTSD) exhibit deficits in autonomic functioning. While PTSD rates are twice as high in women compared to men, sex differences in autonomic functioning are relatively unknown among trauma-exposed populations. The current study used a prospective design to examine sex differences in posttraumatic autonomic functioning. METHODS: 192 participants were recruited from emergency departments following trauma exposure (Mean age = 35.88, 68.2% female). Skin conductance was measured in the emergency department; fear conditioning was completed two weeks later and included measures of blood pressure (BP), heart rate (HR), and high frequency heart rate variability (HF-HRV). PTSD symptoms were assessed 8 weeks after trauma. RESULTS: 2-week systolic BP was significantly higher in men, while 2-week HR was significantly higher in women, and a sex by PTSD interaction suggested that women who developed PTSD demonstrated the highest HR levels. Two-week HF-HRV was significantly lower in women, and a sex by PTSD interaction suggested that women with PTSD demonstrated the lowest HF-HRV levels. Skin conductance response in the emergency department was associated with 2-week HR and HF-HRV only among women who developed PTSD. CONCLUSIONS: Our results indicate that there are notable sex differences in autonomic functioning among trauma-exposed individuals. Differences in sympathetic biomarkers (BP and HR) may have implications for cardiovascular disease risk given that

sympathetic arousal is a mechanism implicated in this risk among PTSD populations. Future research examining differential pathways between PTSD and cardiovascular risk among men versus women is warranted.

Gastroenterology

Madill-Thomsen KS, **Abouljoud M**, Bhati C, Ciszek M, Durlik M, Feng S, Foroncewicz B, **Francis I**, Grąt M, Jurczyk K, Klintmalm G, Krasnodębski M, McCaughan G, Miquel R, Montano-Loza A, **Moonka D**, Mucha K, Myślak M, Pączek L, Perkowska-Ptasińska A, Piecha G, Reichman T, Sanchez-Fueyo A, Tronina O, Wawrzynowicz-Syczewska M, Więcek A, Zieniewicz K, and Halloran PF. The molecular phenotypes of injury, steatohepatitis, and fibrosis in liver transplant biopsies in the INTERLIVER study. *Am J Transplant* 2021; Epub ahead of print. PMID: 34780106. Full Text

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To extend previous molecular analyses of rejection in liver transplant biopsies in the INTERLIVER study (ClinicalTrials.gov #NCT03193151), the present study aimed to define the gene expression selective for parenchymal injury, fibrosis, and steatohepatitis. We analyzed genome-wide microarray measurements from 337 liver transplant biopsies from 13 centers. We examined expression of genes previously annotated as increased in injury and fibrosis using principal component analysis (PCA). PC1 reflected parenchymal injury and related inflammation in the early posttransplant period, slowly regressing over many months. PC2 separated early injury from late fibrosis. Positive PC3 identified a distinct mildly inflamed state correlating with histologic steatohepatitis. Injury PCs correlated with liver function and histologic abnormalities. A classifier trained on histologic steatohepatitis predicted histologic steatohepatitis with cross-validated AUC=0.83, and was associated with pathways reflecting metabolic abnormalities distinct from fibrosis. PC2 predicted histologic fibrosis (AUC=0.80), as did a molecular fibrosis classifier (AUC=0.74). The fibrosis classifier correlated with matrix remodeling pathways with minimal overlap with those selective for steatohepatitis, although some biopsies had both. Genome-wide assessment of liver transplant biopsies can not only detect molecular changes induced by rejection but also those correlating with parenchymal injury, steatohepatitis, and fibrosis, offering potential insights into disease mechanisms for primary diseases.

Gastroenterology
Younossi ZM, Yilmaz Y, Yu ML, Wai-Sun Wong V, Fernandez MC, Isakov VA, Duseja AK, Mendez-Sanchez N, Eguchi Y, Bugianesi E, Burra P, George J, Fan JG, Papatheodoridis GV, Chan WK, Alswat K, Saeed HS, Singal AK, Romero-Gomez M, **Gordon SC**, Roberts SK, El Kassas M, Sr., Kugelmas M, Ong JP, Alqahtani S, Ziayee M, Lam B, Younossi I, Racila A, Henry L, and Stepanova M. Clinical and Patient Reported Outcomes from Patients with Non-alcoholic Fatty Liver Disease Across the World: Data from the Global NASH/NAFLD Registry. *Clin Gastroenterol Hepatol* 2021; Epub ahead of print. PMID: 34768009. Full Text

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BACKGROUND: Globally, nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease. We assessed clinical presentation and patient-reported outcomes (PROs) among NAFLD patients from different countries. METHODS: Clinical, laboratory and PRO data (CLDQ-NASH, FACIT-F, WPAI) were collected from NAFLD patients seen in real-world practices and enrolled in the Global NAFLD/NASH Registry (GNR) encompassing 18 countries in 6 Global Burden of Disease (GBD) super-regions. RESULTS: Across the GBD super-regions, NAFLD patients (n=5691) were oldest in Latin America and Eastern Europe, youngest in South Asia. Most males were enrolled in Southeast and South Asia sites. Latin America and South Asia had the highest employment rates (>60%). Rates of cirrhosis varied (12-21%); highest in North Africa/Middle East and Eastern Europe. Rates of metabolic syndrome components varied: 20-25% in South Asia, 60-80% in Eastern Europe. CLDQ-NASH and FACIT-F PRO scores were lower in NAFLD patients than general population norms (all p<0.001). Across the super-regions, the lowest PRO scores were seen in Eastern Europe and North Africa/Middle East. In multivariate analysis adjusted for enrollment region, independent predictors of lower PRO scores included younger age, female gender, and non-hepatic comorbidities including fatigue (p<0.01). Patients whose fatigue scores improved over time experienced a substantial PRO improvement. Nearly 8% of GNR patients had lean BMI with fewer metabolic syndrome components, fewer comorbidities, less cirrhosis, and significantly better PRO scores (p<0.01). CONCLUSION: NAFLD patients seen in real-world practices in different countries experience high comorbidity burden and impaired quality of life. Future research using global data will enable more precise management and treatment strategies for these patients.

Gastroenterology
Shen B, Kochhar GS, Rubin DT, Kane SV, Navaneethan U, Bernstein CN, Cross RK, Sugita A, **Schairer J**, Kiran RP, Fleshner P, McCormick JT, D'Hoore A, Shah SA, Farraye FA, Kariv R, Liu X, Rosh J, Chang S, Scherl E, Schwartz DA, Kotze PG, Bruining DH, Philpott J, Abraham B, Segal J, Sedano R, Kayal M, Bentley-Hibbert S, Tarabar D, El-Hachem S, Sehgal P, Picoraro JA, Vermeire S, Sandborn WJ, Silverberg MS, and Pardi DS. Treatment of pouchitis, Crohn's disease, cuffitis, and other inflammatory disorders of the pouch: consensus guidelines from the International Ileal Pouch Consortium. *Lancet Gastroenterol Hepatol* 2021; Epub ahead of print. PMID: 34774224. Request Article

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Pouchitis, Crohn's disease of the pouch, cuffitis, polyps, and extraintestinal manifestations of inflammatory bowel disease are common inflammatory disorders of the ileal pouch. Acute pouchitis is treated with oral antibiotics and chronic pouchitis often requires anti-inflammatory therapy, including the use of biologics. Aetiological factors for secondary pouchitis should be evaluated and managed accordingly. Crohn's disease of the pouch is usually treated with biologics and its stricturing and fistulising complications can be treated with endoscopy or surgery. The underlying cause of cuffitis determines treatment strategies. Endoscopic polypectomy is recommended for large, symptomatic inflammatory polyps and polyps in the cuff. The management principles of extraintestinal manifestations of inflammatory bowel disease in patients with pouches are similar to those in patients without pouches.

Graduate Medical Education

Owusu IA, **Passalacqua KD**, Mirabelli C, Lu J, Young V, Hosmillo M, Quaye O, Goodfellow I, Ward V, and Wobus CE. Akt plays differential roles during the life cycles of acute and persistent murine norovirus strains in macrophages. *J Virol* 2021; Epub ahead of print. PMID: 34787460. Request Article

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Akt (Protein kinase B) is a key signaling protein in eukaryotic cells that controls many cellular processes such as glucose metabolism and cell proliferation for survival. As obligate intracellular pathogens, viruses modulate host cellular processes, including Akt signaling, for optimal replication. The mechanisms by which viruses modulate Akt and the resulting effects on the infectious cycle differ widely depending on the virus. In this study, we explored the effect of Akt serine 473 phosphorylation (p-Akt) during murine norovirus (MNV) infection. p-Akt increased during infection of murine macrophages with acute MNV-1 and persistent CR3 and CR6 strains. Inhibition of Akt with MK2206, an inhibitor of all three isoforms of Akt (Akt1/2/3), reduced infectious virus progeny of all three virus strains. This reduction was due to decreased

viral genome replication (CR3), defective virus assembly (MNV-1), or diminished cellular egress (CR3 and CR6) in a virus strain-dependent manner. Collectively, our data demonstrate that Akt activation increases in macrophages during the later stages of the MNV infectious cycle, which may enhance viral infection in unique ways for different virus strains. The data, for the first time, indicate a role for Akt signaling in viral assembly and highlight additional phenotypic differences between closely related MNV strains. Importance Human noroviruses (HNoV) are a leading cause of viral gastroenteritis, resulting in high annual economic burden and morbidity; yet there are no small animal models supporting productive HNoV infection, or robust culture systems producing cell culture-derived virus stocks. As a result, research on drug discovery and vaccine development against norovirus infection has been challenging, and no targeted antivirals or vaccines against HNoV are approved. On the other hand, murine norovirus (MNV) replicates to high titers in cell culture and is a convenient and widespread model in norovirus research. Our data demonstrate the importance of Akt signaling during the late stage of the MNV life cycle. Notably, the effect of Akt signaling on genome replication, virus assembly and cellular egress is virus strain specific, highlighting the diversity of biological phenotypes despite small genetic variability among norovirus strains. This study is the first to demonstrate a role for Akt in viral assembly.

Hematology-Oncology

Bazhenova L, Minchom A, Viteri S, Bauml JM, Ignatius Ou SH, **Gadgeel SM**, Trigo JM, Backenroth D, Li T, Londhe A, Mahadevia P, and Girard N. Comparative clinical outcomes for patients with advanced NSCLC harboring EGFR exon 20 insertion mutations and common EGFR mutations. *Lung Cancer* 2021; 162:154-161. PMID: 34818606. Full Text

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INTRODUCTION: Real-world clinical outcomes in patients with advanced NSCLC harboring EGFR exon 20 insertion (exon20ins) mutations have not been extensively studied. We conducted a retrospective cohort study to assess the clinical outcomes of EGFR exon20ins compared with common EGFR (cEGFR) mutations. METHODS: Adults with advanced NSCLC harboring any EGFR mutations in the NSCLC Flatiron registry (2011 through May 2020) were included. To compare the relative prognosis (prognostic value) of exon20ins vs cEGFR, real-world overall survival (rwOS) was the primary endpoint. Separately, to compare the relative response to tyrosine kinase inhibitor (TKI) treatment (predictive value), real-world progression-free survival (rwPFS) was the primary endpoint. RESULTS: For the prognostic value analysis, 3014 patients with EGFR mutant NSCLC (cEGFR, n = 2833; EGFR exon20ins, n = 181) were eligible. The median (95% CI) rwOS was 16.2 (11.04-19.38) months in the EGFR exon20ins cohort vs 25.5 (24.48-27.04) months in the cEGFR cohort (adjusted HR, 1.75 [1.45-2.13]; p < 0.0001); 5-year rwOS was 8% and 19%, respectively. For the predictive value analysis, 2825 patients received TKI treatment and were eligible (cEGFR, n = 2749; EGFR exon20ins, n = 76). The median (95% CI) rwPFS from start of the first TKI was 2.9 (2.14-3.91) months in the EGFR exon20ins cohort vs 10.5 (10.05-10.94) months in the cEGFR cohort (adjusted HR, 2.69 [2.05-3.54]; p < 0001). Among patients with EGFR exon20ins, the most common prescribed first-line therapy was platinum-based chemotherapy (61.3%) followed by EGFR TKIs (21.5%); second-line treatments were varied, with no clear standard of care. CONCLUSIONS: Patients with EGFR exon20ins have poor prognosis and receive little benefit from EGFR TKI treatment. More effective therapies are needed in this difficult-to-treat population.

Hematology-Oncology
Benitz S, and **Crawford H**. Discovery of the pancreatic basal cell: a new candidate for an adult stem cell emerges. *Gut* 2021; Epub ahead of print. PMID: 34732543. Full Text

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Hematology-Oncology
Hoogenboom WS, Alamuri TT, McMahon DM, **Balanchivadze N**, **Dabak V**, Mitchell WB, Morrone KB, Manwani D, and Duong TQ. Clinical outcomes of COVID-19 in patients with sickle cell disease and sickle cell trait: A critical appraisal of the literature. *Blood Rev* 2021; Epub ahead of print.:100911. PMID: 34838342. Full Text

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Individuals with sickle cell disease (SCD) and sickle cell trait (SCT) have many risk factors that could make them more susceptible to COVID-19 critical illness and death compared to the general population. With a growing body of literature in this field, a comprehensive review is needed. We reviewed 71 COVID-19-related studies conducted in 15 countries and published between January 1, 2020, and October 15, 2021, including a combined total of over 2000 patients with SCD and nearly 2000 patients with SCT. Adults with SCD typically have a mild to moderate COVID-19 disease course, but also a 2- to 7-fold increased risk of COVID-19-related hospitalization and a 1.2-fold increased risk of COVID-19-related death as compared to adults without SCD, but not compared to controls with similar comorbidities and end-organ damage. There is some evidence that persons with SCT have increased risk of COVID-19-related hospitalization and death although more studies with risk-stratification and properly matched controls are needed to confirm these findings. While the literature suggests that most children with SCD and COVID-19 have mild disease and low risk of death, some children with SCD, especially those with SCD-related comorbidities, are more likely to be hospitalized and require escalated care than children without SCD. However, children with SCD are less likely to experience COVID-19-related severe illness and death compared to adults with or without SCD. SCD-directed therapies such as transfusion and hydroxyurea may be associated with better COVID-19 outcomes, but prospective studies are needed for confirmation. While some studies have reported favorable short-term outcomes for COVID-19 patients with SCD and SCT, the long-term effects of SARS-CoV-2 infection are unknown and may affect individuals with SCD and SCT differently from the general population. Important focus areas for future research should include multi-center studies with larger sample sizes, assessment of hemoglobin genotype and SCD-modifying therapies on COVID-19 outcomes, inclusion of case-matched controls that account for the unique sample characteristics of SCD and SCT populations, and longitudinal assessment of post-COVID-19 symptoms.

Hematology-Oncology
Martens K, Ulrich GR, Ranby KW, and Kilbourn K. What Matters Most? Predictors of Quality of Life and Life Satisfaction Among Young Breast Cancer Survivors. *Cancer Nurs* 2021; 44(6):E727-e734. PMID: 34694091. Full Text

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BACKGROUND: Younger breast cancer survivors face unique challenges, and research is needed to better understand how to optimize their quality of life (QoL) and satisfaction with life (SwL). OBJECTIVE: The aim of this study was to examine a biopsychosocial model of QoL and SwL in young breast cancer survivors. Biological, psychological, and social/practical factors were hypothesized to be associated with both distressing and adaptive reactions during survivorship, which in turn were hypothesized to be associated with QoL and SwL. METHODS: Young (age = 19-45 years at diagnosis) breast cancer survivors (N = 284) completed an online survey assessing demographic and biopsychosocial factors, QoL, and SwL. Latent variables were created for adaptive and distressing reactions, and structural equation modeling was used to test the hypothesized relationships. RESULTS: The model fit the data ($\chi 2(100) = 332.92$, $P < .001$, comparative fit index = 0.86, root mean square error of approximation = 0.09, standardized root mean square residual = 0.05) and accounted for large proportions of variance in QoL ($R2 = 0.86$) and SwL ($R2 = 0.62$). Social support, parenting concerns, and fertility concerns each significantly predicted adjustment. Adaptive reactions positively predicted SwL ($\beta = 0.58$, $P < .001$) but not QoL. Distressing reactions negatively predicted SwL ($\beta = -0.26$, $P < .01$) and QoL ($\beta = -0.87$, $P < .001$). CONCLUSIONS: Adjustment in survivorship mediated the association of social support, parenting concerns, and fertility concerns on QoL and SwL in young breast cancer survivors. IMPLICATIONS FOR PRACTICE: To support the psychological adjustment of young breast cancer survivors, attention should be given to survivors' social context including survivors' available social support and their concerns about fertility and parenting.

Hematology-Oncology

Schmidt AL, Tucker MD, Bakouny Z, Labaki C, Hsu CY, Shyr Y, Armstrong AJ, Beer TM, Bijjula RR, Bilen MA, Connell CF, Dawsey SJ, Faller B, Gao X, Gartrell BA, Gill D, Gulati S, Halabi S, **Hwang C**, Joshi M, Khaki AR, Menon H, Morris MJ, Puc M, Russell KB, Shah NJ, Sharifi N, Shaya J, Schweizer MT, Steinharter J, Wulff-Burchfield EM, Xu W, Zhu J, Mishra S, Grivas P, Rini BI, Warner JL, Zhang T, Choueiri TK, Gupta S, and McKay RR. Association Between Androgen Deprivation Therapy and Mortality Among Patients With Prostate Cancer and COVID-19. *JAMA Netw Open* 2021; 4(11). PMID: 34767021. Full Text

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Oregon Health and Science University Knight Cancer Institute, Portland.
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Winship Cancer Institute of Emory University, Atlanta, Georgia.
Penn State Cancer Institute, Hershey, Pennsylvania.
Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio.
Missouri Baptist Medical Center, St Louis.
Massachusetts General Hospital, Boston.
Montefiore Einstein College of Medicine, Bronx, New York.
Intermountain Healthcare, Salt Lake City, Utah.
University of Cincinnati College of Medicine, Cincinnati, Ohio.
Henry Ford Cancer Institute, Henry Ford Hospital, Detroit, Michigan.
University of Washington, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle.
Stanford University, Stanford, California.
Memorial Sloan Kettering Cancer Center, New York, New York.
Virtua Health Network, Marlton, New Jersey.
Tallahassee Memorial Healthcare, Tallahassee, Florida.
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IMPORTANCE: Androgen deprivation therapy (ADT) has been theorized to decrease the severity of SARS-CoV-2 infection in patients with prostate cancer owing to a potential decrease in the tissue-based expression of the SARS-CoV-2 coreceptor transmembrane protease, serine 2 (TMPRSS2). OBJECTIVE: To examine whether ADT is associated with a decreased rate of 30-day mortality from SARS-CoV-2

infection among patients with prostate cancer. DESIGN, SETTING, AND PARTICIPANTS: This cohort study analyzed patient data recorded in the COVID-19 and Cancer Consortium registry between March 17, 2020, and February 11, 2021. The consortium maintains a centralized multi-institution registry of patients with a current or past diagnosis of cancer who developed COVID-19. Data were collected and managed using REDCap software hosted at Vanderbilt University Medical Center in Nashville, Tennessee. Initially, 1228 patients aged 18 years or older with prostate cancer listed as their primary malignant neoplasm were included; 122 patients with a second malignant neoplasm, insufficient follow-up, or low-quality data were excluded. Propensity matching was performed using the nearest-neighbor method with a 1:3 ratio of treated units to control units, adjusted for age, body mass index, race and ethnicity, Eastern Cooperative Oncology Group performance status score, smoking status, comorbidities (cardiovascular, pulmonary, kidney disease, and diabetes), cancer status, baseline steroid use, COVID-19 treatment, and presence of metastatic disease. EXPOSURES: Androgen deprivation therapy use was defined as prior bilateral orchiectomy or pharmacologic ADT administered within the prior 3 months of presentation with COVID-19. MAIN OUTCOMES AND MEASURES: The primary outcome was the rate of all-cause 30-day mortality after COVID-19 diagnosis for patients receiving ADT compared with patients not receiving ADT after propensity matching. RESULTS: After exclusions, 1106 patients with prostate cancer (before propensity score matching: median age, 73 years [IQR, 65-79 years]; 561 (51%) self-identified as non-Hispanic White) were included for analysis. Of these patients, 477 were included for propensity score matching (169 who received ADT and 308 who did not receive ADT). After propensity matching, there was no significant difference in the primary end point of the rate of all-cause 30-day mortality (OR, 0.77; 95% CI, 0.42-1.42). CONCLUSIONS AND RELEVANCE: Findings from this cohort study suggest that ADT use was not associated with decreased mortality from SARS-CoV-2 infection. However, large ongoing clinical trials will provide further evidence on the role of ADT or other androgen-targeted therapies in reducing COVID-19 infection severity.

Hospital Medicine

Hanigan S, Kong X, Haymart B, Kline-Rogers E, **Kaatz S**, **Krol G**, **Shah V**, Ali MA, Almany S, Kozlowski J, Froehlich J, and Barnes G. Standard Versus Higher Intensity Anticoagulation for Patients With Mechanical Aortic Valve Replacement and Additional Risk Factors for Thromboembolism. *Am J Cardiol* 2021; 159:100-106. PMID: 34656311. Full Text

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Current guidelines recommend targeting an international normalized ratio (INR) of 2.5 to 3.5 for patients with mechanical aortic valve replacement (AVR) and additional risk factors for thromboembolic events. Available literature supporting the higher intensity (INR) goal is lacking. We aimed to evaluate the association of standard and higher intensity anticoagulation on outcomes in this patient population. The Michigan Anticoagulation Quality Improvement Initiative database was used to identify patients with mechanical AVR and at least one additional risk factor. Patients were classified into 2 groups based on INR goal: standard-intensity (INR goal 2.5) or higher-intensity (INR goal 3.0). Cox-proportional hazard model was used to calculate adjusted hazard ratios. One hundred and forty-six patients were identified of whom 110 (75.3%) received standard-intensity anticoagulation and 36 (24.7%) received higher intensity anticoagulation. Standard-intensity patients were older and more likely to be on aspirin. Atrial fibrillation was the most common additional risk factor for inclusion. The primary outcome of thromboembolic events, bleeding, or all-cause death was 13.9 and 19.5/100-person-years in the standard-intensity and higher

intensity groups, respectively (adjusted HR 2.58, 95% confidence interval 1.28 to 5.18). Higher-intensity anticoagulation was significantly associated with any bleeding (adjusted HR 2.52, 95% confidence interval 1.27 to 5.00) and there were few thromboembolic events across both groups (5 events total). These results challenge current guideline recommendations for anticoagulation management of mechanical AVR in patients with additional risk factors.

Hospital Medicine
Li P, Zhao W, **Kaatz S**, **Latack K**, **Schultz L**, and **Poisson L**. Factors Associated With Risk of Postdischarge Thrombosis in Patients With COVID-19. *JAMA Netw Open* 2021; 4(11). PMID: 34807256. Full Text

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IMPORTANCE: COVID-19 is associated with a high incidence of thrombotic events; however, the need for extended thromboprophylaxis after hospitalization remains unclear. OBJECTIVE: To quantify the rate of postdischarge arterial and venous thromboembolism in patients with COVID-19, identify the factors associated with the risk of postdischarge venous thromboembolism, and evaluate the association of postdischarge anticoagulation use with venous thromboembolism incidence. DESIGN, SETTING, AND PARTICIPANTS: This is a cohort study of adult patients hospitalized with COVID-19 confirmed by a positive SARS-CoV-2 test. Eligible patients were enrolled at 5 hospitals of the Henry Ford Health System from March 1 to November 30, 2020. Data analysis was performed from April to June 2021. EXPOSURES: Anticoagulant therapy after discharge. MAIN OUTCOMES AND MEASURES: New onset of symptomatic arterial and venous thromboembolic events within 90 days after discharge from the index admission for COVID-19 infection were identified using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes. RESULTS: In this cohort study of 2832 adult patients hospitalized with COVID-19, the mean (SD) age was 63.4 (16.7) years (IQR, 53-75 years), and 1347 patients (47.6%) were men. Thirty-six patients (1.3%) had postdischarge venous thromboembolic events (16 pulmonary embolism, 18 deep vein thrombosis, and 2 portal vein thrombosis). Fifteen (0.5%) postdischarge arterial thromboembolic events were observed (1 transient ischemic attack and 14 acute coronary syndrome). The risk of venous thromboembolism decreased with time (Mann-Kendall trend test, P < .001), with a median (IQR) time to event of 16 (7-43) days. There was no change in the risk of arterial thromboembolism with time (Mann-Kendall trend test, P = .37), with a median (IQR) time to event of 37 (10-63) days. Patients with a history of venous thromboembolism (odds ratio [OR], 3.24; 95% CI, 1.34-7.86), peak dimerized plasmin fragment D (D-dimer) level greater than 3 μg/mL (OR, 3.76; 95% CI, 1.86-7.57), and predischarge C-reactive protein level greater than 10 mg/dL (OR, 3.02; 95% CI, 1.45-6.29) were more likely to experience venous thromboembolism after discharge. Prescriptions for therapeutic anticoagulation at discharge were associated with reduced incidence of venous thromboembolism (OR, 0.18; 95% CI, 0.04-0.75; P = .02). CONCLUSIONS AND RELEVANCE: Although extended thromboprophylaxis in unselected patients with COVID-19 is not supported, these findings suggest that postdischarge anticoagulation may be considered for high-risk patients who have a history of venous thromboembolism, peak D-dimer level greater than 3 μg/mL, and predischarge C-reactive protein level greater than 10 mg/dL, if their bleeding risk is low.

Hospital Medicine
Rothberg MB, Hamilton A, Greene MT, Fox J, Lisheba O, Milinovich A, Gautier TN, Kim P, **Kaatz S**, and Hu B. Derivation and Validation of a Risk Factor Model to Identify Medical Inpatients at Risk for Venous Thromboembolism. *Thromb Haemost* 2021; Epub ahead of print. PMID: 34784645. Full Text

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BACKGROUND: Venous thromboembolism (VTE) prophylaxis is recommended for hospitalized medical patients at high risk for VTE. Multiple risk assessment models exist, but few have been compared in large data sets. METHODS: We constructed a derivation cohort using 6 years of data from 13 hospitals to identify risk factors associated with developing VTE within 14 days of admission. VTE was identified using a complex algorithm combining administrative codes and clinical data. We developed a multivariable prediction model and applied it to 2 validation cohorts: a temporal cohort, including two additional years and a cross-validation, in which we refit the model excluding one hospital at a time, and applied the refitted model to the holdout hospital. Performance was evaluated using the C-statistic. RESULTS: The derivation cohort included 160,928 patients with a 14-day VTE rate of 0.79%. The final multivariable model contained 13 patient risk factors. The model had an optimism corrected C-statistic of 0.80 and good calibration. The temporal validation cohort included 55,301 patients, with a VTE rate of 0.74%. Based on the c-statistic, the Cleveland Clinic Model (CCM) outperformed the Padua model (0.76 vs. 0.72, p<0.01). The CCM was more sensitive (65.8% vs. 60.4%, p=0.05) and more specific (74.9% vs. 71.4%, p<.001), with higher positive (1.9% vs. 1.5%, p<.001) and negative predictive values (99.7% vs. 99.6%, p=0.01). C-statistics for the CCM at individual hospitals ranged from 0.64 to 0.76. CONCLUSION: A new VTE risk assessment model outperformed the Padua model. After further validation it could be recommended for widespread use.

Hypertension and Vascular Research
Bryson TD, and **Harding P**. Prostaglandin E2 EP receptors in cardiovascular disease: An update. *Biochem Pharmacol* 2021; 195:114858. PMID: 34822808. Request Article

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This review article provides an update for the role of prostaglandin E2 receptors (EP1, EP2, EP3 and EP4) in cardiovascular disease. Where possible we have reported citations from the last decade although this was not possible for all of the topics covered due to the paucity of publications. The authors have attempted to cover the subjects of ischemia-reperfusion injury, arrhythmias, hypertension, novel protein binding partners of the EP receptors and their pathophysiological significance, and cardiac regeneration. These latter two topics bring studies of the EP receptors into new and exciting areas of research that are just beginning to be explored. Where there is peer-reviewed literature, the authors have placed particular emphasis on clinical studies although these are limited in number.

Infectious Diseases
Axfors C, Janiaud P, Schmitt AM, Van't Hooft J, Smith ER, Haber NA, Abayomi A, Abduljalil M, Abdulrahman A, Acosta-Ampudia Y, Aguilar-Guisado M, Al-Beidh F, Alejandria MM, Alfonso RN, Ali M, AlQahtani M, AlZamrooni A, Anaya JM, Ang MAC, Aomar IF, Argumanis LE, Averyanov A, Baklaushev VP, Balionis O, Benfield T, Berry S, Birocco N, Bonifacio LB, Bowen AC, Bown A, Cabello-Gutierrez C, Camacho B, Camacho-Ortiz A, Campbell-Lee S, **Cao DH**, Cardesa A, Carnate JM, Castillo GJJ, Cavallo R, Chowdhury FR, Chowdhury FUH, Ciccone G, Cingolani A, Climacosa FMM, Compernolle V, Cortez CFN, Costa Neto A, D'Antico S, Daly J, Danielle F, Davis JS, De Rosa FG, Denholm JT, Denkinger CM, Desmecht D, Díaz-Coronado JC, Díaz Ponce-Medrano JA, Donneau AF, Dumagay TE, Dunachie S, Dungog CC, Erinoso O, Escasa IMS, Estcourt LJ, Evans A, Evasan ALM, Fareli CJ, Fernandez-Sanchez V, Galassi C, Gallo JE, Garcia PJ, Garcia PL, Garcia JA, Garigliany M, Garza-Gonzalez E, Gauiran DTV, Gaviria García PA, Giron-Gonzalez JA, Gómez-Almaguer D, Gordon AC, Gothot A, Grass Guaqueta JS, Green C, Grimaldi D, Hammond NE, Harvala H, Heralde FM, Herrick J, Higgins AM, Hills TE, **Hines J**, Holm K, Hoque A, Hoste E, Ignacio JM, Ivanov AV, Janssen M, **Jennings JH**, Jha V, King RAN,

Kjeldsen-Kragh J, Klenerman P, **Kotecha A**, Krapp F, Labanca L, Laing E, Landin-Olsson M, Laterre PF, Lim LL, Lim J, Ljungquist O, Llaca-Díaz JM, López-Robles C, López-Cárdenas S, Lopez-Plaza I, Lucero JAC, Lundgren M, Macías J, Maganito SC, Malundo AFG, Manrique RD, Manzini PM, Marcos M, Marquez I, Martínez-Marcos FJ, Mata AM, McArthur CJ, McQuilten ZK, McVerry BJ, Menon DK, Meyfroidt G, Mirasol MAL, Misset B, Molton JS, Mondragon AV, Monsalve DM, Moradi Choghakabodi P, Morpeth SC, Mouncey PR, Moutschen M, Müller-Tidow C, **Murphy E**, Najdovski T, Nichol AD, Nielsen H, Novak RM, O'Sullivan MVN, Olalla J, Osibogun A, Osikomaiya B, Oyonarte S, Pardo-Oviedo JM, Patel MC, Paterson DL, Peña-Perez CA, Perez-Calatayud AA, Pérez-Alba E, Perkina A, Perry N, Pouladzadeh M, Poyato I, Price DJ, Quero AKH, Rahman MM, Rahman MS, **Ramesh M**, Ramírez-Santana C, Rasmussen M, Rees MA, Rego E, Roberts JA, Roberts DJ, Rodríguez Y, Rodríguez-Baño J, Rogers BA, Rojas M, Romero A, Rowan KM, Saccona F, Safdarian M, Santos MCM, Sasadeusz J, Scozzari G, Shankar-Hari M, **Sharma G**, Snelling T, Soto A, Tagayuna PY, **Tang A**, **Tatem G**, Teofili L, Tong SYC, Turgeon AF, Veloso JD, Venkatesh B, Ventura-Enriquez Y, Webb SA, Wiese L, Wikén C, Wood EM, Yusubalieva GM, Zacharowski K, Zarychanski R, Khanna N, Moher D, Goodman SN, Ioannidis JPA, and Hemkens LG. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis* 2021; 21(1):1170. PMID: 34800996. Full Text

BACKGROUND: Convalescent plasma has been widely used to treat COVID-19 and is under investigation in numerous randomized clinical trials, but results are publicly available only for a small number of trials. The objective of this study was to assess the benefits of convalescent plasma treatment compared to placebo or no treatment and all-cause mortality in patients with COVID-19, using data from all available randomized clinical trials, including unpublished and ongoing trials (Open Science Framework, https://doi.org/10.17605/OSF.IO/GEHFX). METHODS: In this collaborative systematic review and meta-analysis, clinical trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform), the Cochrane COVID-19 register, the LOVE database, and PubMed were searched until April 8, 2021. Investigators of trials registered by March 1, 2021, without published results were contacted via email. Eligible were ongoing, discontinued and completed randomized clinical trials that compared convalescent plasma with placebo or no treatment in COVID-19 patients, regardless of setting or treatment schedule. Aggregated mortality data were extracted from publications or provided by investigators of unpublished trials and combined using the Hartung-Knapp-Sidik-Jonkman random effects model. We investigated the contribution of unpublished trials to the overall evidence. RESULTS: A total of 16,477 patients were included in 33 trials (20 unpublished with 3190 patients, 13 published with 13,287 patients). 32 trials enrolled only hospitalized patients (including 3 with only intensive care unit patients). Risk of bias was low for 29/33 trials. Of 8495 patients who received convalescent plasma, 1997 died (23%), and of 7982 control patients, 1952 died (24%). The combined risk ratio for all-cause mortality was 0.97 (95% confidence interval: 0.92; 1.02) with between-study heterogeneity not beyond chance ($I(2) = 0\%$). The RECOVERY trial had 69.8% and the unpublished evidence 25.3% of the weight in the meta-analysis. CONCLUSIONS: Convalescent plasma treatment of patients with COVID-19 did not reduce all-cause mortality. These results provide strong evidence that convalescent plasma treatment for patients with COVID-19 should not be used outside of randomized trials. Evidence synthesis from collaborations among trial investigators can inform both evidence generation and evidence application in patient care.

Internal Medicine

Bhattarai S, Mackeyev Y, **Venkatesulu BP**, Krishnan S, and Singh PK. CXC chemokine receptor 4 (CXCR4) targeted gold nanoparticles potently enhance radiotherapy outcomes in breast cancer. *Nanoscale* 2021; 13(45):19056-19065. PMID: 34757363. Request Article

Department of Experimental Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA. Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL, USA. singh.pankaj@mayo.edu. Department of internal medicine, Henry Ford Hospital, Detroit, MI, USA.

CXC chemokine receptor 4 (CXCR4) is overexpressed on most breast cancer cell surfaces including triple negative breast cancer (TNBC) which lacks traditional receptor overexpression. We targeted gold

nanoparticles (GNPs) to this receptor via conjugation to anti-CXCR4 antibody (cGNPs). Irradiation of cells treated with cGNPs compared to PEGylated GNPs (pGNPs) resulted in more prominent radiosensitization of MDA-MB-231 cells with abundant CXCR4 overexpression than HTB-123 cells with moderate and MCF-7 cells with minimal CXCR4 overexpression. Overexpression of CXCR4 facilitated improved cellular internalization of cGNPs and irradiation of internalized cGNPs resulted in more unrepaired DNA double strand breaks and increased the production of oxygen free radicals compared to irradiation with non-internalized pGNPs. In a murine TNBC xenograft model, CXCR4 targeting potently increased tumor regrowth delay following radiation compared to radiation in the presence of pGNPs or vehicle alone. CXCR4 targeted GNPs enhance the efficacy of TNBC radiotherapy by increasing oxidative stress and DNA damage.

Internal Medicine

Calvo-Ayala E, **Procopio V**, **Papukhyan H**, and Nair GB. Performance of Automated Telemetry in Diagnosing QT Prolongation in Critically Ill Patients. *Am J Crit Care* 2021; 30(6):466-470. PMID: 34719703. Full Text

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Vince Procopio is a critical care pharmacy specialist, Department of Pharmacy, Henry Ford Macomb Hospital, Clinton Township, Michigan.
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Girish B. Nair is an attending physician, Division of Pulmonary, Critical Care and Sleep Medicine, William Beaumont Hospital and an associate professor, Department of Internal Medicine, Oakland University William Beaumont School of Medicine.

BACKGROUND: QT prolongation increases the risk of ventricular arrhythmia and is common among critically ill patients. The gold standard for QT measurement is electrocardiography. Automated measurement of corrected QT (QTc) by cardiac telemetry has been developed, but this method has not been compared with electrocardiography in critically ill patients. OBJECTIVE: To compare the diagnostic performance of QTc values obtained with cardiac telemetry versus electrocardiography. METHODS: This prospective observational study included patients admitted to intensive care who had an electrocardiogram ordered simultaneously with cardiac telemetry. Demographic data and QTc determined by electrocardiography and telemetry were recorded. Bland-Altman analysis was done, and correlation coefficient and receiver operating characteristic (ROC) coefficient were calculated. RESULTS: Fifty-one data points were obtained from 43 patients (65% men). Bland-Altman analysis revealed poor agreement between telemetry and electrocardiography and evidence of fixed and proportional bias. Area under the ROC curve for QTc determined by telemetry was 0.9 ($P < .001$) for a definition of prolonged QT as QTc ≥ 450 milliseconds in electrocardiography (sensitivity, 88.89%; specificity, 83.33%; cutoff of 464 milliseconds used). Correlation between the 2 methods was only moderate ($r = 0.6$, $P < .001$). CONCLUSIONS: QTc determination by telemetry has poor agreement and moderate correlation with electrocardiography. However, telemetry has an acceptable area under the curve in ROC analysis with tolerable sensitivity and specificity depending on the cutoff used to define prolonged QT. Cardiac telemetry should be used with caution in critically ill patients.

Internal Medicine

Gupta K, **Viacava RC**, Jain V, Kakar TS, **Jesse M**, and Virani SS. Trends in Patient-Recalled Targets for Cardiovascular Risk Factors in Ambulatory US Adults With Diabetes Mellitus (from National Health and Nutrition Examination Survey). *Am J Cardiol* 2021; Epub ahead of print. PMID: 34839899. Full Text

Division of General Internal Medicine, Department of Medicine, Henry Ford Hospital, Detroit, Michigan.
Department of Medicine, Cleveland Clinic, Cleveland, Ohio.
Department of Medicine, William Beaumont Hospital, Royal Oak, Michigan.
Division of General Internal Medicine, Department of Medicine, Henry Ford Hospital, Detroit, Michigan; Transplant Institute, Henry Ford Health System, Detroit, Michigan.

Section of Cardiology and Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, Texas; Health Policy, Quality & Informatics Program, Health Services Research and Development Center for Innovations in Quality, Effectiveness, and Safety (IQuESt), Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; Section of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas.

Internal Medicine

Hanigan S, Kong X, Haymart B, Kline-Rogers E, **Kaatz S**, **Krol G**, **Shah V**, Ali MA, Almany S, Kozlowski J, Froehlich J, and Barnes G. Standard Versus Higher Intensity Anticoagulation for Patients With Mechanical Aortic Valve Replacement and Additional Risk Factors for Thromboembolism. *Am J Cardiol* 2021; 159:100-106. PMID: 34656311. Full Text

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Department of Cardiovascular Medicine, Huron Valley Sinai Hospital, Commerce Township, Michigan.
Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; Institute of Healthcare Policy and Innovation, University of Michigan, Ann Arbor, Michigan.

Current guidelines recommend targeting an international normalized ratio (INR) of 2.5 to 3.5 for patients with mechanical aortic valve replacement (AVR) and additional risk factors for thromboembolic events. Available literature supporting the higher intensity (INR) goal is lacking. We aimed to evaluate the association of standard and higher intensity anticoagulation on outcomes in this patient population. The Michigan Anticoagulation Quality Improvement Initiative database was used to identify patients with mechanical AVR and at least one additional risk factor. Patients were classified into 2 groups based on INR goal: standard-intensity (INR goal 2.5) or higher-intensity (INR goal 3.0). Cox-proportional hazard model was used to calculate adjusted hazard ratios. One hundred and forty-six patients were identified of whom 110 (75.3%) received standard-intensity anticoagulation and 36 (24.7%) received higher intensity anticoagulation. Standard-intensity patients were older and more likely to be on aspirin. Atrial fibrillation was the most common additional risk factor for inclusion. The primary outcome of thromboembolic events, bleeding, or all-cause death was 13.9 and 19.5/100-person-years in the standard-intensity and higher intensity groups, respectively (adjusted HR 2.58, 95% confidence interval 1.28 to 5.18). Higher-intensity anticoagulation was significantly associated with any bleeding (adjusted HR 2.52, 95% confidence interval 1.27 to 5.00) and there were few thromboembolic events across both groups (5 events total). These results challenge current guideline recommendations for anticoagulation management of mechanical AVR in patients with additional risk factors.

Nephrology

Axfors C, Janiaud P, Schmitt AM, Van't Hooft J, Smith ER, Haber NA, Abayomi A, Abduljalil M, Abdulrahman A, Acosta-Ampudia Y, Aguilar-Guisado M, Al-Beidh F, Alejandria MM, Alfonso RN, Ali M, AlQahtani M, AlZamrooni A, Anaya JM, Ang MAC, Aomar IF, Argumanis LE, Averyanov A, Baklaushev VP, Balionis O, Benfield T, Berry S, Birocco N, Bonifacio LB, Bowen AC, Bown A, Cabello-Gutierrez C, Camacho B, Camacho-Ortiz A, Campbell-Lee S, **Cao DH**, Cardesa A, Carnate JM, Castillo GJJ, Cavallo R, Chowdhury FR, Chowdhury FUH, Ciccone G, Cingolani A, Climacosa FMM, Compernolle V, Cortez CFN, Costa Neto A, D'Antico S, Daly J, Danielle F, Davis JS, De Rosa FG, Denholm JT, Denkinger CM, Desmecht D, Díaz-Coronado JC, Díaz Ponce-Medrano JA, Donneau AF, Dumagay TE, Dunachie S, Dungog CC, Erinoso O, Escasa IMS, Estcourt LJ, Evans A, Evasan ALM, Fareli CJ, Fernandez-Sanchez V, Galassi C, Gallo JE, Garcia PJ, Garcia PL, Garcia JA, Garigliany M, Garza-Gonzalez E, Gauiran DTV, Gaviria García PA, Giron-Gonzalez JA, Gómez-Almaguer D, Gordon AC, Gothot A, Grass Guaqueta JS, Green C, Grimaldi D, Hammond NE, Harvala H, Heralde FM, Herrick J, Higgins AM, Hills TE, **Hines J**,

Holm K, Hoque A, Hoste E, Ignacio JM, Ivanov AV, Janssen M, **Jennings JH**, Jha V, King RAN, Kjeldsen-Kragh J, Klenerman P, **Kotecha A**, Krapp F, Labanca L, Laing E, Landin-Olsson M, Laterre PF, Lim LL, Lim J, Ljungquist O, Llaca-Díaz JM, López-Robles C, López-Cárdenas S, Lopez-Plaza I, Lucero JAC, Lundgren M, Macías J, Maganito SC, Malundo AFG, Manrique RD, Manzini PM, Marcos M, Marquez I, Martínez-Marcos FJ, Mata AM, McArthur CJ, McQuilten ZK, McVerry BJ, Menon DK, Meyfroidt G, Mirasol MAL, Misset B, Molton JS, Mondragon AV, Monsalve DM, Moradi Choghakabodi P, Morpeth SC, Mouncey PR, Moutschen M, Müller-Tidow C, **Murphy E**, Najdovski T, Nichol AD, Nielsen H, Novak RM, O'Sullivan MVN, Olalla J, Osibogun A, Osikomaiya B, Oyonarte S, Pardo-Oviedo JM, Patel MC, Paterson DL, Peña-Perez CA, Perez-Calatayud AA, Pérez-Alba E, Perkina A, Perry N, Pouladzadeh M, Poyato I, Price DJ, Quero AKH, Rahman MM, Rahman MS, **Ramesh M**, Ramírez-Santana C, Rasmussen M, Rees MA, Rego E, Roberts JA, Roberts DJ, Rodríguez Y, Rodríguez-Baño J, Rogers BA, Rojas M, Romero A, Rowan KM, Saccona F, Safdarian M, Santos MCM, Sasadeusz J, Scozzari G, Shankar-Hari M, **Sharma G**, Snelling T, Soto A, Tagayuna PY, **Tang A**, **Tatem G**, Teofili L, Tong SYC, Turgeon AF, Veloso JD, Venkatesh B, Ventura-Enriquez Y, Webb SA, Wiese L, Wikén C, Wood EM, Yusubalieva GM, Zacharowski K, Zarychanski R, Khanna N, Moher D, Goodman SN, Ioannidis JPA, and Hemkens LG. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis* 2021; 21(1):1170. PMID: 34800996. Full Text

BACKGROUND: Convalescent plasma has been widely used to treat COVID-19 and is under investigation in numerous randomized clinical trials, but results are publicly available only for a small number of trials. The objective of this study was to assess the benefits of convalescent plasma treatment compared to placebo or no treatment and all-cause mortality in patients with COVID-19, using data from all available randomized clinical trials, including unpublished and ongoing trials (Open Science Framework, https://doi.org/10.17605/OSF.IO/GEHFX). METHODS: In this collaborative systematic review and meta-analysis, clinical trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform), the Cochrane COVID-19 register, the LOVE database, and PubMed were searched until April 8, 2021. Investigators of trials registered by March 1, 2021, without published results were contacted via email. Eligible were ongoing, discontinued and completed randomized clinical trials that compared convalescent plasma with placebo or no treatment in COVID-19 patients, regardless of setting or treatment schedule. Aggregated mortality data were extracted from publications or provided by investigators of unpublished trials and combined using the Hartung-Knapp-Sidik-Jonkman random effects model. We investigated the contribution of unpublished trials to the overall evidence. RESULTS: A total of 16,477 patients were included in 33 trials (20 unpublished with 3190 patients, 13 published with 13,287 patients). 32 trials enrolled only hospitalized patients (including 3 with only intensive care unit patients). Risk of bias was low for 29/33 trials. Of 8495 patients who received convalescent plasma, 1997 died (23%), and of 7982 control patients, 1952 died (24%). The combined risk ratio for all-cause mortality was 0.97 (95% confidence interval: 0.92; 1.02) with between-study heterogeneity not beyond chance ($I(2) = 0\%$). The RECOVERY trial had 69.8% and the unpublished evidence 25.3% of the weight in the meta-analysis. CONCLUSIONS: Convalescent plasma treatment of patients with COVID-19 did not reduce all-cause mortality. These results provide strong evidence that convalescent plasma treatment for patients with COVID-19 should not be used outside of randomized trials. Evidence synthesis from collaborations among trial investigators can inform both evidence generation and evidence application in patient care.

Nephrology

Mohiuddin N, **Frinak S**, and **Yee J**. Sodium-based osmotherapy for hyponatremia in acute decompensated heart failure. *Heart Fail Rev* 2021; Epub ahead of print. PMID: 34767112. Full Text

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Acute decompensated heart failure (ADHF) accounts for more than 1 million hospital admissions annually and is associated with high morbidity and mortality. Decongestion with removal of increased total body sodium and total body water are goals of treatment. Acute kidney injury (AKI) or chronic kidney disease

(CKD) is present in two-thirds of patients with ADHF. The pathophysiology of ADHF and AKI is bidirectional and synergistic. AKI and CKD complicate the management of ADHF by decreasing diuretic efficiency and excretion of sodium and water. Among patients hospitalized with ADHF, hyponatremia is the most common electrolyte abnormality and is classically encountered with volume overload. ADHF represents an additional therapeutic challenge particularly when oligoanuria is present. Predilution continuous venovenous hemofiltration with sodium-based osmotherapy can safely increase plasma sodium concentration without deleteriously increasing total body sodium. We present a detailed methodology that addresses the issue of hypervolemic hyponatremia in patients with ADHF and AKI.

Neurology
Bambakidis T, Dekker SE, Williams AM, Biesterveld BE, Bhatti UF, Liu B, Li Y, Pickell Z, **Buller B**, and Alam HB. Early Treatment With A Single Dose of Mesenchymal Stem Cell Derived Extracellular Vesicles Modulates The Brain Transcriptome to Create Neuroprotective Changes In A Porcine Model of Traumatic Brain Injury and Hemorrhagic Shock. *Shock* 2021; Epub ahead of print. PMID: 34798633. Full Text

Department of Surgery, University of Michigan, Ann Arbor, MI, United States Department of Microbiology, Oregon State University, Corvallis, OR, United States Department of Medicine, Oregon Health & Science University, Portland, OR, United States Department of Neurology, Henry Ford Hospital, Detroit, MI, United States.

BACKGROUND: Cell-based therapies using mesenchymal stem cell derived extracellular vesicles (EVs) improve neurologic outcomes in animal models of traumatic brain injury (TBI), stroke, and hemorrhage. Using a porcine 7-day survival model of TBI and hemorrhagic shock (HS), we previously demonstrated that EV-treatment was associated with reduced brain lesion size, neurologic severity score, and cerebral inflammation. However, the underlying cellular and genomic mechanisms remain poorly defined. We hypothesize that EV treatment modulates the brain transcriptome to enhance neuroprotection and neurorestoration following TBI+HS. METHODS: Swine were subjected to severe TBI (8-mm cortical impact) and HS (40% blood volume). After 1 hour of shock, animals were randomized (n=4/group) to treatment with either lactated Ringer's (LR) or LR+EV. Both groups received fluid resuscitation after 2 hours of shock, and autologous packed red blood cells 5 hours later.After 7-days, brains were harvested and RNA-sequencing was performed. The transcriptomic data was imported into the iPathway pipeline for bioinformatics analyses. RESULTS: 5,273 genes were differentially expressed in the LR+EV group vs. LR alone (total 9,588 measured genes). Genes with the greatest upregulation were involved in synaptic transmission and neuronal development and differentiation, while downregulated genes were involved in inflammation. GO-terms experiencing the greatest modulation were involved in inflammation, brain development, and cell adhesion. Pathway analysis revealed significant modulation in the glutamatergic and GABAergic systems. Network analysis revealed downregulation of inflammation, and upregulation of neurogenesis, and neuron survival and differentiation. CONCLUSIONS: In a porcine model of TBI+HS, EV treatment was associated with an attenuation of cerebral inflammatory networks and a promotion of neurogenesis and neuroplasticity. These transcriptomic changes could explain the observed neuroprotective and neurorestorative properties associated with EV treatment.

Neurology
Zaidi SK, Ahmed F, Alkhatabi H, **Hoda MN**, and Al-Qahtani M. Nebulization of low-dose s-nitrosoglutathione in diabetic stroke enhances benefits of reperfusion and prevents post-thrombolysis hemorrhage. *Biomolecules* 2021; 11(11). PMID: Not assigned. Full Text

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The COVID-19 pandemic has escalated the occurrence of hypoxia including thrombotic stroke worldwide, for which nitric oxide (NO) therapy seems very promising and translatable. Therefore, various modes/routes of NO-delivery are now being tested in different clinical trials for safer, faster, and more effective interventions against ischemic insults. Intravenous (IV) infusion of S-Nitrosoglutathione (GSNO), the major endogenous molecular pool of NO, has been reported to protect against mechanical cerebral ischemia-reperfusion (IR); however, it has been never tested in any kind of “clinically” relevant

thromboembolic stroke models with or without comorbidities and in combination with the thrombolytic reperfusion therapy. Moreover, “IV-effects” of higher dose of GSNO following IR-injury have been contradicted to augment stroke injury. Herein, we tested the hypothesis that nebulization of low-dose GSNO will not alter blood pressure (BP) and will mitigate stroke injury in diabetic mice via enhanced cerebral blood flow (CBF) and brain tissue oxygenation (PbtO2). GSNO-nebulization (200 µg/kgbwt) did not alter BP, but augmented the restoration of CBF, improved behavioral outcomes and reduced stroke injury. Moreover, GSNO-nebulization increased early reoxygenation of brain tissue/PbtO2 as measured at 6.5 h post-stroke following thrombolytic reperfusion, and enervated unwanted effects of late thrombolysis in diabetic stroke. We conclude that the GSNO-nebulization is safe and effective for enhancing collateral microvascular perfusion in the early hours following stroke. Hence, nebulized-GSNO therapy has the potential to be developed and translated into an affordable field therapy against ischemic events including strokes, particularly in developing countries with limited healthcare infrastructure.

Neurosurgery
Nassiri F, Wang JZ, Au K, Barnholtz-Sloan J, Jenkinson MD, Drummond K, **Zhou Y**, **Snyder JM**, Brastianos P, Santarius T, Suppiah S, **Poisson L**, Gaillard F, Rosenthal M, Kaufmann T, Tsang D, Aldape K, and Zadeh G. Consensus core clinical data elements for meningiomas. *Neuro Oncol* 2021; Epub ahead of print. PMID: 34791428. Full Text

MacFeeters Hamilton Neuro-Oncology Program, Princess Margaret Cancer Centre, University Health Network and University of Toronto, ON, Canada.
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Department of Radiology, The Royal Melbourne Hospital, Melbourne, Australia.
Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia.
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BACKGROUND: With increasing molecular analyses of meningiomas, there is a need to harmonize language used to capture clinical data across centers to ensure that molecular alterations are appropriately linked to clinical variables of interest. Here the International Consortium on Meningiomas presents a set of core and supplemental meningioma-specific Common Data Elements (CDEs) to facilitate comparative and pooled analyses. METHODS: The generation of CDEs followed the four-phase process similar to other National Institute of Neurological Disorders and Stroke (NINDS) CDE projects: discovery, internal validation, external validation, and distribution. RESULTS: The CDEs were organized into patient- and tumor-level modules. In total, 17 core CDEs (10 patient-level and 7-tumour-level) as well as 14 supplemental CDEs (7 patient-level and 7 tumour-level) were defined and described. These CDEs are now made publicly available for dissemination and adoption. CONCLUSIONS: CDEs provide a framework for discussion in the neuro-oncology community that will facilitate data sharing for collaborative research projects and aid in developing a common language for comparative and pooled analyses. The meningioma-specific CDEs presented here are intended to be dynamic parameters that evolve with time and The Consortium welcomes international feedback for further refinement and implementation of these CDEs.

Neurosurgery
Rahman MM, Alam MM, Alfaifi SYM, Asiri AM, and **Ali MM**. Sensitive Detection of Thiourea Hazardous Toxin with Sandwich-Type Nafion/CuO/ZnO Nanospikes/Glassy Carbon Composite Electrodes. *Polymers (Basel)* 2021; 13(22). PMID: 34833297. Full Text

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In this research study, we developed a voltammetric electrochemical sensor probe with a copolymer Nafion (Sulfonated Tetrafluoroethylene-based Fluoro-polymer) decorated with hydrothermally prepared sandwich-type CuO/ZnO nanospikes (NSs) onto a glassy carbon electrode (GCE) for reliable thiourea (TU) detection. The detailed characterizations in terms of structural morphology, binding energy, elemental compositions, grain size and crystallinity for synthesized NSs were performed by field emission scanning electron microscopy (FESEM), X-ray photoelectron spectroscopy (XPS), energy-dispersive X-ray spectroscopy (EDS) and X-ray diffraction (XRD) analysis, respectively. The differential pulse voltammetric (DPV) analysis for TU showed good linearity at current-versus-TU concentration on the calibration plot in the 0.15~1.20 mM range, which is defined as a dynamic detection range (LDR) of TU in a phosphate buffer solution. Considering the slope of LDR over the GCE-coated NSs surface area (0.0316 cm(2)), the TU sensor sensitivity (0.4122 μA μM(-1) cm(-2)) was obtained. Besides this, the low limit (LOD) for TU detection was calculated and found to be 23.03 ± 1.15 μM. The fabricated Nafion/CuO/ZnO NSs/GCE sensor probe was created as a reliable sensor based on reproducibility, interference effect, stability and response time. Real bio-samples were investigated and the results confirm the anticipated reliability of the TU sensor probe. Thus, this is a noble way to develop enzyme-free electrochemical sensors that could be an alternative approach for the detection of chemicals in the field of enzyme-free biosensor development technology.

Neurosurgery

Reddy J, Fonseca MAS, Corona RI, Nameki R, Segato Dezem F, Klein IA, Chang H, Chaves-Moreira D, Afeyan LK, **Malta TM**, Lin X, Abbasi F, Font-Tello A, Sabedot T, Cejas P, Rodríguez-Malavé N, Seo JH, Lin DC, Matulonis U, Karlan BY, Gayther SA, Pasaniuc B, Gusev A, **Noushmehr H**, Long H, Freedman ML, Drapkin R, Young RA, Abraham BJ, and Lawrenson K. Predicting master transcription factors from pan-cancer expression data. *Sci Adv* 2021; 7(48). PMID: 34818047. Full Text

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Nursing
Draus C, Mianecki TB, Musgrove H, **Bastien DJ**, Greggs D, Halash C, Bellamy CL, **Lewis A**, and Mackenzie W. Perceptions of Nurses Who Are Second Victims in a Hospital Setting. *J Nurs Care Qual* 2021; Epub ahead of print. PMID: 34775418. Full Text

Center for Nursing Research and Evidence-Based Practice (Drs Draus and Mianecki), Surgical Intensive Care Unit (Ms Musgrove), B4/F1 (Ms Greggs), Medical Intensive Care Unit (Ms Halash), Labor and Delivery, High Risk Antepartum (Dr Bellany), and Labor and Delivery/I3 High Risk Antenatal (Ms Mackenzie), Henry Ford Hospital, Detroit, Michigan; Henry Ford Health System, Detroit, Michigan (Dr Bastien); and Henry Ford Health System, West Bloomfield, Michigan (Ms Lewis).

BACKGROUND: Second victims (SVs) are health care workers traumatized by unanticipated, adverse patient events. These experiences can have personal and professional effects on SVs. Research indicates that SVs experience inadequate support following adverse events. PURPOSE: To determine the prevalence of nurses who identified as SVs and their awareness and use of supportive resources. METHODS: A convenience sample of nurses was surveyed, and SV responses were compared with those who did not identify as a SV. Responses were analyzed using nonparametric methods. RESULTS: One hundred fifty-nine (44.3%) of 359 participants identified as SVs. There was a significant relationship between work tenure and SVs (P = .009). A relationship was found between SVs and awareness and use of support resources, with debriefing being the preferred method after an event. CONCLUSIONS: Adverse events trigger emotional trauma in SVs who require administrative awareness, support, and follow-up to minimize psychological trauma in the clinical nurse.

Nursing
Maceri J. Positive outcomes of a surgical progressive care unit for patients following head and neck cancer surgery. *Nurs Manage* 2021; 52(11):34-40. PMID: 34723884. Full Text

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Obstetrics, Gynecology and Women's Health Services
Yoon J, Fitzgerald H, Wang Y, Wang Q, Vergalasova I, **Elshaikh MA**, **Dimitrova I**, Damast S, Li JY, Fields EC, Beriwal S, Keller A, Kidd EA, Usoz M, Jolly S, Jaworski E, Leung EW, Donovan E, Taunk NK, Chino J, Natesan D, Russo AL, Lea JS, Albuquerque KV, Lee LJ, and Hathout L. Does prophylactic para-aortic lymphatic irradiation improve outcomes in women with stage IIIC1 endometrial carcinoma? A multi-institutional pooled analysis. *Pract Radiat Oncol* 2021; Epub ahead of print. PMID: 34822999. Full Text

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PURPOSE: To evaluate the impact of prophylactic PALN RT on clinical outcomes in patients with FIGO 2018 stage IIIC1 EC. MATERIALS/METHODS: A multi-institutional retrospective study included patients with FIGO 2018 stage IIIC1 EC status post surgical staging, lymph node assessment followed by adjuvant chemotherapy and radiotherapy using various sequencing regimens. Overall survival (OS) and recurrence-free survival (RFS) rates were estimated by Kaplan-Meier method. Univariable and multivariable analysis were performed by Cox proportional hazard models for RFS/OS. In addition, propensity score matching were used to estimate the effect of the radiation field extent on survival outcomes. RESULTS: A total of 378 patients were included with a median follow-up of 45.8 months. Pelvic RT was delivered to 286 patients while 92 patients received pelvic and PALN RT. The estimated OS and RFS rates at 5 years for the entire cohort were 80% and 69%, respectively. There was no difference in the 5-year OS (77% vs. 87%, p=0.47) and RFS rates (67% vs. 70%, p=0.78) between patients treated with pelvic RT and those with pelvic and prophylactic PALN RT, respectively. After propensity score matching, the estimated Hazard Ratios (HR) of prophylactic PALN RT vs. pelvic RT were 1.50 (95% CI = (0.71, 3.19), p-value = 0.28) for OS and 1.24 (95% CI = (0.64, 2.42), p-value = 0.51) for RFS suggesting that prophylactic PALN RT does not improve survival outcomes. Distant recurrence was the most common site of first recurrence, and the extent of RT field was not associated with the site of first recurrence (P=0.79). CONCLUSIONS: Prophylactic PALN RT was not significantly associated with improved survival outcomes in stage IIIC1 EC. Distant metastases remain the most site of failure despite routine use of systemic chemotherapy, new therapeutic approaches are necessary to optimize the outcomes for women with stage IIIC1 EC.

Ophthalmology and Eye Care Services

Shabani H, Zrenner E, **Rathbun DL**, and Hosseinzadeh Z. Classification of pseudocalcium visual responses from mouse retinal ganglion cells. *Visual Neuroscience* 2021; 38. PMID: Not assigned. Full Text

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Recently, a detailed catalog of 32 retinal ganglion cell (RGC) visual response patterns in mouse has emerged. However, the 10,000 samples required for this catalog-based on fluorescent signals from a calcium indicator dye-are much harder to acquire from the extracellular spike train recordings underlying our bionic vision research. Therefore, we sought to convert spike trains into pseudocalcium signals so that our data could be directly matched to the 32 predefined, calcium signal-based groups. A microelectrode array (MEA) was used to record spike trains from mouse RGCs of 29 retinas. Visual stimuli were adapted from the Baden et al. study; including moving bars, full-field contrast and temporal frequency chirps, and black-white and UV-green color flashes. Spike train histograms were converted into pseudocalcium traces with an OGB-1 convolution kernel. Response features were extracted using sparse principal components analysis to match each RGC to one of the 32 RGC groups. These responses mapped onto of the 32 previously described groups; however, some of the groups remained unmatched. Thus, adaptation of the Baden et al. methodology for MEA recordings of spike trains instead of calcium recordings was partially successful. Different classification methods, however, will be needed to define clear RGC groups from MEA data for our bionic vision research. Nevertheless, others may pursue a pseudocalcium approach to reconcile spike trains with calcium signals. This work will help to guide them on the limitations and potential pitfalls of such an approach.

Ophthalmology and Eye Care Services

Shen SR, Boese EA, Clark CP, Man X, **Nika M**, and Moroi SE. Acute Angle-Closure Crisis Secondary to Topiramate-Induced Ciliochoroidal Effusion With Underlying Plateau Iris Configuration. *Journal of Diagnostic Medical Sonography* 2021; 37(6):528-534. PMID: Not assigned. Full Text

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Objective: The development of ciliochoroidal effusions and secondary acute angle-closure crisis (AACC) is an uncommon side effect of topiramate, a common antiepileptic now FDA-approved for migraine prophylaxis. The mechanisms that underlie the development of ciliochoroidal effusions after topiramate use remain unclear. Materials and Methods: Ultrasound biomicroscopy (UBM) was also performed in all participants after stopping topiramate. Results: Six patient cases are presented with medication-induced AACC following the initiation or escalation of topiramate. Ciliochoroidal effusions were confirmed by gray-scale sonography in all patients at presentation. The images revealed either plateau iris configuration or atypical plateau iris configuration. Plateau iris configuration is defined by presence of an anteriorly rotated ciliary body processes and an absent posterior sulcus. Atypical plateau iris configuration refers to when the iris inserts directly into the ciliary body face. This case series, of medication-induced angle-closure crisis, suggests that plateau iris configuration is a shared anatomical feature in the development of topiramate-induced ciliochoroidal effusions.

Orthopedics/Bone and Joint Center

Ali SA, Pastrello C, **Kaur N**, Peffers MJ, Ormseth MJ, and Jurisica I. A Network Biology Approach to Understanding the Tissue-Specific Roles of Non-Coding RNAs in Arthritis. *Front Endocrinol (Lausanne)* 2021; 12:744747. PMID: 34803912. Full Text

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Discovery of non-coding RNAs continues to provide new insights into some of the key molecular drivers of musculoskeletal diseases. Among these, microRNAs have received widespread attention for their roles in osteoarthritis and rheumatoid arthritis. With evidence to suggest that long non-coding RNAs and circular RNAs function as competing endogenous RNAs to sponge microRNAs, the net effect on gene expression in specific disease contexts can be elusive. Studies to date have focused on elucidating individual long non-coding-microRNA-gene target axes and circular RNA-microRNA-gene target axes, with a paucity of data integrating experimentally validated effects of non-coding RNAs. To address this gap, we curated recent studies reporting non-coding RNA axes in chondrocytes from human osteoarthritis and in fibroblast-like synoviocytes from human rheumatoid arthritis. Using an integrative computational biology approach, we then combined the findings into cell- and disease-specific networks for in-depth interpretation. We highlight some challenges to data integration, including non-existent naming conventions and out-of-date databases for non-coding RNAs, and some successes exemplified by the International Molecular Exchange Consortium for protein interactions. In this perspective article, we suggest that data integration is a useful in silico approach for creating non-coding RNA networks in

arthritis and prioritizing interactions for further in vitro and in vivo experimentation in translational research.

Orthopedics/Bone and Joint Center
Buckley PJ, **Jildeh TR**, **Abbas MJ**, and Okoroha KR. Acromioclavicular Joint Reconstruction with Recessed Clavicular Implant Technique Guide. *Arthroscopy Techniques* 2021; 10(11):e2577-e2582. PMID: Not assigned. Full Text

P.J. Buckley, Henry Ford Hospital, Department of Orthopaedic Surgery, 2799 W. Grand Blvd, Detroit, MI, United States

Acromioclavicular (AC) joint injuries are common and often require operative intervention. Although there are many described surgical techniques, there remains a lack of consensus on the optimal technique. The purpose of this Technical Note is to provide our preferred method of AC reconstruction with a recessed clavicular implant and semitendinosus allograft, which mitigates hardware pain associated with arthroscopic techniques.

Orthopedics/Bone and Joint Center
Jiang EX, **Fisk FE**, **Taliaferro K**, and Pahuta MA. Calculating Ex-ante Utilities From the modified Japanese Orthopedic Association Score: A Prerequisite for Quantifying the Value of Care for Cervical Myelopathy. *Spine (Phila Pa 1976)* 2021; Epub ahead of print. PMID: 34812194. Full Text

Department of Orthopedic Surgery, Henry Ford Hospital, Detroit, MI Division of Orthopedic Surgery, McMaster University, Hamilton, ON, Canada.

STUDY DESIGN: General population utility valuation study. OBJECTIVE: The aim of this study was to develop a technique for calculating utilities from the modified Japanese Orthopedic Association (mJOA) Score. SUMMARY OF BACKGROUND DATA: The ability to calculate quality-adjusted life-years (QALYs) for degenerative cervical myelopathy (DCM) would enhance treatment decision making and facilitate economic analysis. QALYs are calculated using utilities. METHODS: We recruited a sample of 760 adults from a market research panel. Using an online discrete choice experiment, participants rated eight choice sets based on mJOA health states. A multiattribute utility function was estimated using a mixed multinomial-logit regression model. The sample was partitioned into a training set used for model fitting and validation set used for model evaluation. RESULTS: The regression model demonstrated good predictive performance on the validation set with an area under the curve of 0.81 (95% confidence interval: 0.80-0.82)). The regression model was used to develop a utility scoring rubric for the mJOA. Regression results revealed that participants did not regard all mJOA domains as equally important. The rank order of importance was (in decreasing order): lower extremity motor function, upper extremity motor function, sphincter dysfunction, upper extremity sensation. CONCLUSION: This study provides a simple technique for converting the mJOA score to utilities and quantify the importance of mJOA domains. The ability to evaluate QALYs for DCM will facilitate economic analysis and patient counseling. Clinicians should heed these findings and offer treatments that maximize function in the attributes viewed most important by patients.Level of Evidence: 3.

Orthopedics/Bone and Joint Center
Parsons TW, 3rd. The AOA: A Comprehensive House with Compassionate Leaders. Presidential Address to the AOA, June 15, 2020: AOA Critical Issues. *J Bone Joint Surg Am* 2021; 103(21):e85. PMID: 34730564. Full Text

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The American Orthopaedic Association (AOA) is the world's oldest orthopaedic association and it has been responsible for the founding of many prominent organizations as well as The Journal of Bone & Joint Surgery. While the AOA has traditionally focused on academic orthopaedic leadership, the time has come to expand our horizons and look to include all orthopaedic leaders from the wide variety of

leadership roles in which they currently serve.Orthopaedic surgeons who demonstrate compassionate leadership will find that they create stronger, more successful teams. Compassionate leadership is a skill that can be learned, and investing the energy to develop this skill will have a profound impact on our success as orthopaedic surgeons and leaders.

Orthopedics/Bone and Joint Center

Taliaferro K, Rao A, Theologis AA, Cummins D, Callahan M, and Berven SH. Rates and risk factors associated with 30- and 90-day readmissions and reoperations after spinal fusions for adult lumbar degenerative pathology and spinal deformity. *Spine Deform* 2021; Epub ahead of print. PMID: 34846718. Request Article

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PURPOSE: Analyze state databases to determine variables associated with of short-term readmissions and reoperations following thoracolumbar spine fusions for degenerative pathology and spinal deformity. METHODS: Retrospective study of State Inpatient Database (2005-13, CA, NE, NY, FL, NC, UT). INCLUSION CRITERIA: age > 45 years, diagnosis of degenerative spinal deformity, ≥ 3 level posterolateral lumbar spine fusion. EXCLUSION CRITERIA: revision surgery, cervical fusions, trauma, and cancer. Univariate and step-wise multivariate logistic regression analyses were performed to identify independent variables associated with of 30- and 90-day readmissions and reoperations. RESULTS: 12,641 patients were included. All-cause 30- and 90-day readmission rates were 14.6% and 21.1%, respectively. 90-day readmissions were associated with: age > 80 (OR: 1.42), 8 + level fusions (OR: 1.19), hospital length of stay (LOS) > 7 days (OR: 1.43), obesity (OR: 1.29), morbid obesity (OR: 1.66), academic hospital (OR: 1.13), cancer history (OR:1.21), drug abuse (OR: 1.31), increased Charlson Comorbidity index (OR: 1.12), and depression (OR: 1.20). Private insurance (OR: 0.64) and lumbar-only fusions (OR: 0.87) were not associated with 90-day readmissions. All-cause 30- and 90-day reoperation rates were 1.8% and 4.2%, respectively. Variables associated with 90-day reoperations were 8 + level fusions (OR: 1.28), LOS > 7 days (OR: 1.43), drug abuse (OR: 1.68), osteoporosis (OR: 1.26), and depression (OR: 1.23). Circumferential fusion (OR: 0.58) and lumbar-only fusions (OR: 0.68) were not associated with 90-day reoperations. CONCLUSIONS: 30- and 90-day readmission and reoperation rates in thoracolumbar fusions for adult degenerative pathology and spinal deformity may have been underreported in previously published smaller studies. Identification of modifiable risk factors is important for improving quality of care through preoperative optimization.

Orthopedics/Bone and Joint Center

Trompeter N, **Gardinier JD**, DeBarros V, Boggs M, Gangadharan V, Cain WJ, Hurd L, and Duncan RL. Insulin-like growth factor-1 regulates the mechanosensitivity of chondrocytes by modulating TRPV4. *Cell Calcium* 2021; 99:102467. PMID: 34530313. Full Text

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Both mechanical and biochemical stimulation are required for maintaining the integrity of articular cartilage. However, chondrocytes respond differently to mechanical stimuli in osteoarthritic cartilage when biochemical signaling pathways, such as Insulin-like Growth Factor-1 (IGF-1), are altered. The Transient Receptor Potential Vanilloid 4 (TRPV4) channel is central to chondrocyte mechanotransduction and

regulation of cartilage homeostasis. Here, we propose that changes in IGF-1 can modulate TRPV4 channel activity. We demonstrate that physiologic levels of IGF-1 suppress hypotonic-induced TRPV4 currents and intracellular calcium flux by increasing apparent cell stiffness that correlates with actin stress fiber formation. Disruption of F-actin following IGF-1 treatment results in the return of the intracellular calcium response to hypotonic swelling. Using point mutations of the TRPV4 channel at the microtubule-associated protein 7 (MAP-7) site shows that regulation of TRPV4 by actin is mediated via the interaction of actin with the MAP-7 domain of TRPV4. We further highlight that ATP release, a down-stream response to mechanical stimulation in chondrocytes, is mediated by TRPV4 during hypotonic challenge. This response is significantly abrogated with IGF-1 treatment. As chondrocyte mechanosensitivity is greatly altered during osteoarthritis progression, IGF-1 presents as a promising candidate for prevention and treatment of articular cartilage damage.

Otolaryngology – Head and Neck Surgery

Cook A, Modh A, **Ali H**, **Sheqwara J**, **Chang S**, **Ghanem T**, **Momin S**, **Wu V**, **Tam S**, **Money S**, **Han X**, **Fakhoury L**, **Movsas B**, and **Siddiqui F**. Randomized Phase III, Double Blind, Placebo-Controlled Study of Prophylactic Gabapentin for the Reduction of Oral Mucositis Pain During the Treatment of Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; Epub ahead of print. PMID: 34808255. Full Text

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PURPOSE: To determine if prophylactic gabapentin usage in patients undergoing definitive concurrent chemoradiotherapy (chemoRT) for oropharyngeal cancer (OPC) improves treatment-related oral mucositis pain, opioid use, and feeding tube (FT) placement. METHODS AND MATERIALS: This double-blind, randomized phase III study for patients with locally advanced OPC undergoing chemoRT randomly allocated patients to prophylactic gabapentin (600 mg thrice daily) or placebo. The primary endpoint was change in Patient-Reported Oral Mucositis Symptom (PROMS) scores over the entire treatment period (baseline to 6 weeks post-RT follow-up) with higher scores indicating worse outcomes. Opioid requirements, FT placement, and other patient-reported QOL metrics (Functional Assessment of Cancer Therapy-Head and Neck [FACT-HN] and Patient-Reported Outcomes of Common Terminology Criteria for Adverse Events [PRO-CTCAE]) were assessed. Lower scores suggested poorer quality of life (QOL) with the FACT-HN questionnaire, and higher scores suggested worse outcomes with the PRO-CTCAE questionnaire. Questionnaires were administered at baseline, weekly during RT, and at 6-week post-RT follow-up. Repeated measures analysis of variance were used to detect differences in PROMS scores and change in opioid use from baseline. Wilcoxon-rank sum tests were used to compare averages for the other secondary endpoints. A p-value less than .05 was considered statistically significant. RESULTS: Treatment arms were well-balanced overall, including T and N staging and dosimetric variables. There were 58 patients analyzed. No significant difference was found in PROMS scores (mean 29.1, Standard Deviation [SD] 22.5, vs 20.1, SD 16.8, for gabapentin vs placebo, respectively, $p = .11$). The FACT-HN functional well-being index had a significant decrease in scores from baseline to follow-up in the gabapentin arm (median -6, interquartile range [IQR] -10.0 to -0.5, vs -1, IQR -5.5 to 3.0, $p = .03$). PRO-CTCAE scores increased significantly at follow-up for gabapentin (median 6.5, IQR 3.5 to 11.8, vs 1, IQR -2.0 to 6.0, $p = .01$). There was no significant difference in average or change in opioid use. FT placement was significantly higher in the gabapentin arm (62.1% vs 20.7%, $p < .01$). CONCLUSIONS: This study suggests that prophylactic gabapentin is not effective in improving treatment-related oral mucositis symptoms in a select population of patients with OPC undergoing definitive chemoRT.

Pathology and Laboratory Medicine

Axfors C, Janiaud P, Schmitt AM, Van't Hooft J, Smith ER, Haber NA, Abayomi A, Abduljalil M, Abdulrahman A, Acosta-Ampudia Y, Aguilar-Guisado M, Al-Beidh F, Alejandria MM, Alfonso RN, Ali M, AlQahtani M, AlZamrooni A, Anaya JM, Ang MAC, Aomar IF, Argumanis LE, Averyanov A, Baklaushev VP, Balionis O, Benfield T, Berry S, Birocco N, Bonifacio LB, Bowen AC, Bown A, Cabello-Gutierrez C, Camacho B, Camacho-Ortiz A, Campbell-Lee S, **Cao DH**, Cardesa A, Carnate JM, Castillo GJJ, Cavallo R, Chowdhury FR, Chowdhury FUH, Ciccone G, Cingolani A, Climacosa FMM, Compernolle V, Cortez CFN, Costa Neto A, D'Antico S, Daly J, Danielle F, Davis JS, De Rosa FG, Denholm JT, Denkinger CM, Desmecht D, Díaz-Coronado JC, Díaz Ponce-Medrano JA, Donneau AF, Dumagay TE, Dunachie S, Dungog CC, Erinoso O, Escasa IMS, Estcourt LJ, Evans A, Evasan ALM, Fareli CJ, Fernandez-Sanchez V, Galassi C, Gallo JE, Garcia PJ, Garcia PL, Garcia JA, Garigliany M, Garza-Gonzalez E, Gauiran DTV, Gaviria García PA, Giron-Gonzalez JA, Gómez-Almaguer D, Gordon AC, Gothot A, Grass Guaqueta JS, Green C, Grimaldi D, Hammond NE, Harvala H, Heralde FM, Herrick J, Higgins AM, Hills TE, **Hines J**, Holm K, Hoque A, Hoste E, Ignacio JM, Ivanov AV, Janssen M, **Jennings JH**, Jha V, King RAN, Kjeldsen-Kragh J, Klenerman P, **Kotecha A**, Krapp F, Labanca L, Laing E, Landin-Olsson M, Laterre PF, Lim LL, Lim J, Ljungquist O, Llaca-Díaz JM, López-Robles C, López-Cárdenas S, Lopez-Plaza I, Lucero JAC, Lundgren M, Macías J, Maganito SC, Malundo AFG, Manrique RD, Manzini PM, Marcos M, Marquez I, Martínez-Marcos FJ, Mata AM, McArthur CJ, McQuilten ZK, McVerry BJ, Menon DK, Meyfroidt G, Mirasol MAL, Misset B, Molton JS, Mondragon AV, Monsalve DM, Moradi Choghakabodi P, Morpeth SC, Mouncey PR, Moutschen M, Müller-Tidow C, **Murphy E**, Najdovski T, Nichol AD, Nielsen H, Novak RM, O'Sullivan MVN, Olalla J, Osibogun A, Osikomaiya B, Oyonarte S, Pardo-Oviedo JM, Patel MC, Paterson DL, Peña-Perez CA, Perez-Calatayud AA, Pérez-Alba E, Perkina A, Perry N, Pouladzadeh M, Poyato I, Price DJ, Quero AKH, Rahman MM, Rahman MS, **Ramesh M**, Ramírez-Santana C, Rasmussen M, Rees MA, Rego E, Roberts JA, Roberts DJ, Rodríguez Y, Rodríguez-Baño J, Rogers BA, Rojas M, Romero A, Rowan KM, Saccona F, Safdarian M, Santos MCM, Sasadeusz J, Scozzari G, Shankar-Hari M, **Sharma G**, Snelling T, Soto A, Tagayuna PY, **Tang A**, **Tatem G**, Teofili L, Tong SYC, Turgeon AF, Veloso JD, Venkatesh B, Ventura-Enriquez Y, Webb SA, Wiese L, Wikén C, Wood EM, Yusubalieva GM, Zacharowski K, Zarychanski R, Khanna N, Moher D, Goodman SN, Ioannidis JPA, and Hemkens LG. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis* 2021; 21(1):1170. PMID: 34800996. Full Text

BACKGROUND: Convalescent plasma has been widely used to treat COVID-19 and is under investigation in numerous randomized clinical trials, but results are publicly available only for a small number of trials. The objective of this study was to assess the benefits of convalescent plasma treatment compared to placebo or no treatment and all-cause mortality in patients with COVID-19, using data from all available randomized clinical trials, including unpublished and ongoing trials (Open Science Framework, https://doi.org/10.17605/OSF.IO/GEHFX). METHODS: In this collaborative systematic review and meta-analysis, clinical trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform), the Cochrane COVID-19 register, the LOVE database, and PubMed were searched until April 8, 2021. Investigators of trials registered by March 1, 2021, without published results were contacted via email. Eligible were ongoing, discontinued and completed randomized clinical trials that compared convalescent plasma with placebo or no treatment in COVID-19 patients, regardless of setting or treatment schedule. Aggregated mortality data were extracted from publications or provided by investigators of unpublished trials and combined using the Hartung-Knapp-Sidik-Jonkman random effects model. We investigated the contribution of unpublished trials to the overall evidence. RESULTS: A total of 16,477 patients were included in 33 trials (20 unpublished with 3190 patients, 13 published with 13,287 patients). 32 trials enrolled only hospitalized patients (including 3 with only intensive care unit patients). Risk of bias was low for 29/33 trials. Of 8495 patients who received convalescent plasma, 1997 died (23%), and of 7982 control patients, 1952 died (24%). The combined risk ratio for all-cause mortality was 0.97 (95% confidence interval: 0.92; 1.02) with between-study heterogeneity not beyond chance ($I(2) = 0\%$). The RECOVERY trial had 69.8% and the unpublished evidence 25.3% of the weight in the meta-analysis. CONCLUSIONS: Convalescent plasma treatment of patients with COVID-19 did not reduce all-cause mortality. These results provide strong evidence that convalescent plasma treatment for patients with COVID-19 should not be used outside of randomized trials. Evidence synthesis from

collaborations among trial investigators can inform both evidence generation and evidence application in patient care.

Pediatrics

Joseph CL, **Sitarik AR**, **Kim H**, Huffnagle G, Fujimura K, Yong GJM, **Levin AM**, **Zoratti E**, Lynch S, Ownby DR, Lukacs NW, Davidson B, **Barone C**, and **Cole Johnson C**. Infant gut bacterial community composition and food-related manifestation of atopy in early childhood. *Pediatr Allergy Immunol* 2021; Epub ahead of print. PMID: 34811824. Full Text

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BACKGROUND: Immunoglobulin E - mediated food allergy (IgE-FA) has emerged as a global public health concern. Immune dysregulation is an underlying mechanism for IgE-FA, caused by "dysbiosis" of the early intestinal microbiota. We investigated the association between infant gut bacterial composition and food-related atopy at age 3-5 years using a well-characterized birth cohort. METHODS: The study definition of IgE-FA to egg, milk, or peanut was based on physician panel retrospective review of clinical and questionnaire data collected from birth through age 3-5 years. Using 16S rRNA sequencing, we profiled the bacterial gut microbiota present in stool specimens collected at 1 and 6 months of age. RESULTS: Of 447 infants with data for analysis, 44 (9.8%) met physician panel review criteria for IgE-FA to ≥1 of the three allergens. Among children classified as IgE-FA at 3-5 years, infant stool samples showed significantly less diversity of the gut microbiota compared to the samples of children classified as no IgE-FA at age 3-5 years, especially for milk and peanut (all covariate adjusted p's for alpha metrics <0.007). Testing of individual operational taxonomic units (OTUs) revealed 6-month deficiencies in 31 OTUs for IgE-FA compared to no IgE-FA, mostly in the orders Lactobacillales, Bacteroidales, and Clostridiales. CONCLUSIONS: Variations in gut microbial composition in infant stool were associated with a study definition of IgE-FA at 3-5 years of age. This included evidence of a lack of bacterial diversity, deficiencies in specific OTUs, and delayed microbial maturation. Results support dysbiosis in IgE-FA pathogenesis.

Pharmacy

Calvo-Ayala E, **Procopio V**, **Papukhyan H**, and Nair GB. Performance of Automated Telemetry in Diagnosing QT Prolongation in Critically Ill Patients. *Am J Crit Care* 2021; 30(6):466-470. PMID: 34719703. Full Text

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BACKGROUND: QT prolongation increases the risk of ventricular arrhythmia and is common among critically ill patients. The gold standard for QT measurement is electrocardiography. Automated measurement of corrected QT (QTc) by cardiac telemetry has been developed, but this method has not been compared with electrocardiography in critically ill patients. OBJECTIVE: To compare the diagnostic

performance of QTc values obtained with cardiac telemetry versus electrocardiography. METHODS: This prospective observational study included patients admitted to intensive care who had an electrocardiogram ordered simultaneously with cardiac telemetry. Demographic data and QTc determined by electrocardiography and telemetry were recorded. Bland-Altman analysis was done, and correlation coefficient and receiver operating characteristic (ROC) coefficient were calculated. RESULTS: Fifty-one data points were obtained from 43 patients (65% men). Bland-Altman analysis revealed poor agreement between telemetry and electrocardiography and evidence of fixed and proportional bias. Area under the ROC curve for QTc determined by telemetry was 0.9 ($P < .001$) for a definition of prolonged QT as QTc ≥ 450 milliseconds in electrocardiography (sensitivity, 88.89%; specificity, 83.33%; cutoff of 464 milliseconds used). Correlation between the 2 methods was only moderate ($r = 0.6$, $P < .001$). CONCLUSIONS: QTc determination by telemetry has poor agreement and moderate correlation with electrocardiography. However, telemetry has an acceptable area under the curve in ROC analysis with tolerable sensitivity and specificity depending on the cutoff used to define prolonged QT. Cardiac telemetry should be used with caution in critically ill patients.

Public Health Sciences

Axfors C, Janiaud P, Schmitt AM, Van't Hooft J, Smith ER, Haber NA, Abayomi A, Abduljalil M, Abdulrahman A, Acosta-Ampudia Y, Aguilar-Guisado M, Al-Beidh F, Alejandria MM, Alfonso RN, Ali M, AlQahtani M, AlZamrooni A, Anaya JM, Ang MAC, Aomar IF, Argumanis LE, Averyanov A, Baklaushev VP, Balionis O, Benfield T, Berry S, Birocco N, Bonifacio LB, Bowen AC, Bown A, Cabello-Gutierrez C, Camacho B, Camacho-Ortiz A, Campbell-Lee S, **Cao DH**, Cardesa A, Carnate JM, Castillo GJJ, Cavallo R, Chowdhury FR, Chowdhury FUH, Ciccone G, Cingolani A, Climacosa FMM, Compernolle V, Cortez CFN, Costa Neto A, D'Antico S, Daly J, Danielle F, Davis JS, De Rosa FG, Denholm JT, Denkinger CM, Desmecht D, Díaz-Coronado JC, Díaz Ponce-Medrano JA, Donneau AF, Dumagay TE, Dunachie S, Dungog CC, Erinoso O, Escasa IMS, Estcourt LJ, Evans A, Evasan ALM, Fareli CJ, Fernandez-Sanchez V, Galassi C, Gallo JE, Garcia PJ, Garcia PL, Garcia JA, Garigliany M, Garza-Gonzalez E, Gauiran DTV, Gaviria García PA, Giron-Gonzalez JA, Gómez-Almaguer D, Gordon AC, Gothot A, Grass Guaqueta JS, Green C, Grimaldi D, Hammond NE, Harvala H, Heralde FM, Herrick J, Higgins AM, Hills TE, **Hines J**, Holm K, Hoque A, Hoste E, Ignacio JM, Ivanov AV, Janssen M, **Jennings JH**, Jha V, King RAN, Kjeldsen-Kragh J, Klenerman P, **Kotecha A**, Krapp F, Labanca L, Laing E, Landin-Olsson M, Laterre PF, Lim LL, Lim J, Ljungquist O, Llaca-Díaz JM, López-Robles C, López-Cárdenas S, Lopez-Plaza I, Lucero JAC, Lundgren M, Macías J, Maganito SC, Malundo AFG, Manrique RD, Manzini PM, Marcos M, Marquez I, Martínez-Marcos FJ, Mata AM, McArthur CJ, McQuilten ZK, McVerry BJ, Menon DK, Meyfroidt G, Mirasol MAL, Misset B, Molton JS, Mondragon AV, Monsalve DM, Moradi Choghakabodi P, Morpeth SC, Mouncey PR, Moutschen M, Müller-Tidow C, **Murphy E**, Najdovski T, Nichol AD, Nielsen H, Novak RM, O'Sullivan MVN, Olalla J, Osibogun A, Osikomaiya B, Oyonarte S, Pardo-Oviedo JM, Patel MC, Paterson DL, Peña-Perez CA, Perez-Calatayud AA, Pérez-Alba E, Perkina A, Perry N, Pouladzadeh M, Poyato I, Price DJ, Quero AKH, Rahman MM, Rahman MS, **Ramesh M**, Ramírez-Santana C, Rasmussen M, Rees MA, Rego E, Roberts JA, Roberts DJ, Rodríguez Y, Rodríguez-Baño J, Rogers BA, Rojas M, Romero A, Rowan KM, Saccona F, Safdarian M, Santos MCM, Sasadeusz J, Scozzari G, Shankar-Hari M, **Sharma G**, Snelling T, Soto A, Tagayuna PY, **Tang A**, **Tatem G**, Teofili L, Tong SYC, Turgeon AF, Veloso JD, Venkatesh B, Ventura-Enriquez Y, Webb SA, Wiese L, Wikén C, Wood EM, Yusubalieva GM, Zacharowski K, Zarychanski R, Khanna N, Moher D, Goodman SN, Ioannidis JPA, and Hemkens LG. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis* 2021; 21(1):1170. PMID: 34800996. Full Text

BACKGROUND: Convalescent plasma has been widely used to treat COVID-19 and is under investigation in numerous randomized clinical trials, but results are publicly available only for a small number of trials. The objective of this study was to assess the benefits of convalescent plasma treatment compared to placebo or no treatment and all-cause mortality in patients with COVID-19, using data from all available randomized clinical trials, including unpublished and ongoing trials (Open Science Framework, https://doi.org/10.17605/OSF.IO/GEHFX). METHODS: In this collaborative systematic review and meta-analysis, clinical trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform), the Cochrane COVID-19 register, the LOVE database, and PubMed were searched until April 8, 2021. Investigators of trials registered by March 1, 2021, without published results were

contacted via email. Eligible were ongoing, discontinued and completed randomized clinical trials that compared convalescent plasma with placebo or no treatment in COVID-19 patients, regardless of setting or treatment schedule. Aggregated mortality data were extracted from publications or provided by investigators of unpublished trials and combined using the Hartung-Knapp-Sidik-Jonkman random effects model. We investigated the contribution of unpublished trials to the overall evidence. RESULTS: A total of 16,477 patients were included in 33 trials (20 unpublished with 3190 patients, 13 published with 13,287 patients). 32 trials enrolled only hospitalized patients (including 3 with only intensive care unit patients). Risk of bias was low for 29/33 trials. Of 8495 patients who received convalescent plasma, 1997 died (23%), and of 7982 control patients, 1952 died (24%). The combined risk ratio for all-cause mortality was 0.97 (95% confidence interval: 0.92; 1.02) with between-study heterogeneity not beyond chance ($I(2) = 0\%$). The RECOVERY trial had 69.8% and the unpublished evidence 25.3% of the weight in the meta-analysis. CONCLUSIONS: Convalescent plasma treatment of patients with COVID-19 did not reduce all-cause mortality. These results provide strong evidence that convalescent plasma treatment for patients with COVID-19 should not be used outside of randomized trials. Evidence synthesis from collaborations among trial investigators can inform both evidence generation and evidence application in patient care.

Public Health Sciences

Bagher Ebadian H, **Siddiqui F**, **Ghanem A**, **Zhu S**, **Lu M**, **Movsas B**, and **Chetty IJ**. Radiomics outperforms clinical factors in characterizing human papilloma virus (HPV) for patients with oropharyngeal squamous cell carcinomas. *Biomed Phys Eng Express* 2021; Epub ahead of print. PMID: 34781281. Full Text

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Purpose:To utilize radiomic features extracted from CT images to characterize Human Papilloma Virus (HPV) for patients with oropharyngeal cancer squamous cell carcinoma (OPSCC).Methods:One hundred twenty-eight OPSCC patients with known HPV-status (60-HPV+ and 68-HPV-, confirmed by immunohistochemistry-P16-protein testing) were retrospectively studied. Radiomic features (11 feature-categories) were extracted in 3D from contrast-enhanced (CE)-CT images of gross-tumor-volumes using 'in-house' software ('ROdiomiX') developed and validated following the image-biomarker-standardization-initiative (IBSI) guidelines. Six clinical factors were investigated: Age-at-Diagnosis, Gender, Total-Charlson, Alcohol-Use, Smoking-History, and T-Stage. A Least-Absolute-Shrinkage-and-Selection-Operation (Lasso) technique combined with a Generalized-Linear-Model (Lasso-GLM) were applied to perform regularization in the radiomic and clinical feature spaces to identify the ranking of optimal feature subsets with most representative information for prediction of HPV. Lasso-GLM models/classifiers based on clinical factors only, radiomics only, and combined clinical and radiomics (ensemble/integrated) were constructed using random-permutation-sampling. Tests of significance (One-way ANOVA), average Area-Under-Receiver-Operating-Characteristic (AUC), and Positive and Negative Predictive values (PPV and NPV) were computed to estimate the generalization-error and prediction performance of the classifiers.Results:Five clinical factors, including T-stage, smoking status, and age, and 14 radiomic features, including tumor morphology, and intensity contrast were found to be statistically significant discriminators between HPV positive and negative cohorts. Performances for prediction of HPV for the 3 classifiers were: Radiomics-Lasso-GLM: AUC/PPV/NPV=0.789/0.755/0.805; Clinical-Lasso-GLM: 0.676/0.747/0.672, and Integrated/Ensemble-Lasso-GLM: 0.895/0.874/0.844. Results imply that the radiomics-based classifier enabled better characterization and performance prediction of HPV relative to clinical factors, and that the combination of both radiomics and clinical factors yields even higher accuracy characterization and predictive performance.Conclusion:Albeit subject to confirmation in a larger

cohort, this pilot study presents encouraging results in support of the role of radiomic features towards characterization of HPV in patients with OPSCC.

Public Health Sciences

Cook A, Modh A, **Ali H**, **Sheqwara J**, **Chang S**, **Ghanem T**, **Momin S**, **Wu V**, **Tam S**, **Money S**, **Han X**, **Fakhoury L**, **Movsas B**, and **Siddiqui F**. Randomized Phase III, Double Blind, Placebo-Controlled Study of Prophylactic Gabapentin for the Reduction of Oral Mucositis Pain During the Treatment of Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; Epub ahead of print. PMID: 34808255. Full Text

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PURPOSE: To determine if prophylactic gabapentin usage in patients undergoing definitive concurrent chemoradiotherapy (chemoRT) for oropharyngeal cancer (OPC) improves treatment-related oral mucositis pain, opioid use, and feeding tube (FT) placement. METHODS AND MATERIALS: This double-blind, randomized phase III study for patients with locally advanced OPC undergoing chemoRT randomly allocated patients to prophylactic gabapentin (600 mg thrice daily) or placebo. The primary endpoint was change in Patient-Reported Oral Mucositis Symptom (PROMS) scores over the entire treatment period (baseline to 6 weeks post-RT follow-up) with higher scores indicating worse outcomes. Opioid requirements, FT placement, and other patient-reported QOL metrics (Functional Assessment of Cancer Therapy-Head and Neck [FACT-HN] and Patient-Reported Outcomes of Common Terminology Criteria for Adverse Events [PRO-CTCAE]) were assessed. Lower scores suggested poorer quality of life (QOL) with the FACT-HN questionnaire, and higher scores suggested worse outcomes with the PRO-CTCAE questionnaire. Questionnaires were administered at baseline, weekly during RT, and at 6-week post-RT follow-up. Repeated measures analysis of variance were used to detect differences in PROMS scores and change in opioid use from baseline. Wilcoxon-rank sum tests were used to compare averages for the other secondary endpoints. A p-value less than .05 was considered statistically significant. RESULTS: Treatment arms were well-balanced overall, including T and N staging and dosimetric variables. There were 58 patients analyzed. No significant difference was found in PROMS scores (mean 29.1, Standard Deviation [SD] 22.5, vs 20.1, SD 16.8, for gabapentin vs placebo, respectively, p = .11). The FACT-HN functional well-being index had a significant decrease in scores from baseline to follow-up in the gabapentin arm (median -6, interquartile range [IQR] -10.0 to -0.5, vs -1, IQR -5.5 to 3.0, p = .03). PRO-CTCAE scores increased significantly at follow-up for gabapentin (median 6.5, IQR 3.5 to 11.8, vs 1, IQR -2.0 to 6.0, p = .01). There was no significant difference in average or change in opioid use. FT placement was significantly higher in the gabapentin arm (62.1% vs 20.7%, p < .01). CONCLUSIONS: This study suggests that prophylactic gabapentin is not effective in improving treatment-related oral mucositis symptoms in a select population of patients with OPC undergoing definitive chemoRT.

Public Health Sciences

Johnson CC, **Havstad SL**, Ownby DR, **Joseph CLM**, **Sitarik AR**, Biagini Myers J, Gebretsadik T, Hartert TV, Khurana Hershey GK, Jackson DJ, Lemanske RF, Jr., Martin LJ, **Zoratti EM**, Visness CM, Ryan PH, Gold DR, Martinez FD, Miller RL, Seroogy CM, Wright AL, and Gern JE. Pediatric asthma incidence rates in the United States from 1980 to 2017. *J Allergy Clin Immunol* 2021; 148(5):1270-1280. PMID: 33964299. Full Text

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BACKGROUND: Few studies have examined longitudinal asthma incidence rates (IRs) from a public health surveillance perspective. OBJECTIVE: Our aim was to calculate descriptive asthma IRs in children over time with consideration for demographics and parental asthma history. METHODS: Data from 9 US birth cohorts were pooled into 1 population covering the period from 1980 to 2017. The outcome was earliest parental report of a doctor diagnosis of asthma. IRs per 1,000 person-years were calculated. RESULTS: The racial/ethnic backgrounds of the 6,283 children studied were as follows: 55% European American (EA), 25.5% African American (AA), 9.5% Mexican-Hispanic American (MA) and 8.5% Caribbean-Hispanic American (CA). The average follow-up was 10.4 years (SD = 8.5 years; median = 8.4 years), totaling 65,291 person-years, with 1789 asthma diagnoses yielding a crude IR of 27.5 per 1,000 person-years (95% CI = 26.3-28.8). Age-specific rates were highest among children aged 0 to 4 years, notably from 1995 to 1999, with a decline in EA and MA children in 2000 to 2004 followed by a decline in AA and CA children in 2010 to 2014. Parental asthma history was associated with statistically significantly increased rates. IRs were similar and higher in AA and CA children versus lower but similar in EA and MA children. The differential rates by sex from birth through adolescence principally resulted from a decline in rates among males but relatively stable rates among females. CONCLUSIONS: US childhood asthma IRs varied dramatically by age, sex, parental asthma history, race/ethnicity, and calendar year. Higher rates in the 0- to 4-year-olds group, particularly among AA/CA males with a parental history of asthma, as well as changes in rates over time and by demographic factors, suggest that asthma is driven by complex interactions between genetic susceptibility and variation in time-dependent environmental and social factors.

Public Health Sciences

Joseph CL, **Sitarik AR**, **Kim H**, Huffnagle G, Fujimura K, Yong GJM, **Levin AM**, **Zoratti E**, Lynch S, Ownby DR, Lukacs NW, Davidson B, **Barone C**, and **Cole Johnson C**. Infant gut bacterial community composition and food-related manifestation of atopy in early childhood. *Pediatr Allergy Immunol* 2021; Epub ahead of print. PMID: 34811824. Full Text

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BACKGROUND: Immunoglobulin E - mediated food allergy (IgE-FA) has emerged as a global public health concern. Immune dysregulation is an underlying mechanism for IgE-FA, caused by "dysbiosis" of the early intestinal microbiota. We investigated the association between infant gut bacterial composition and food-related atopy at age 3-5 years using a well-characterized birth cohort. METHODS: The study definition of IgE-FA to egg, milk, or peanut was based on physician panel retrospective review of clinical and questionnaire data collected from birth through age 3-5 years. Using 16S rRNA sequencing, we profiled the bacterial gut microbiota present in stool specimens collected at 1 and 6 months of age. RESULTS: Of 447 infants with data for analysis, 44 (9.8%) met physician panel review criteria for IgE-FA

to ≥1 of the three allergens. Among children classified as IgE-FA at 3-5 years, infant stool samples showed significantly less diversity of the gut microbiota compared to the samples of children classified as no IgE-FA at age 3-5 years, especially for milk and peanut (all covariate adjusted p's for alpha metrics <0.007). Testing of individual operational taxonomic units (OTUs) revealed 6-month deficiencies in 31 OTUs for IgE-FA compared to no IgE-FA, mostly in the orders Lactobacillales, Bacteroidales, and Clostridiales. CONCLUSIONS: Variations in gut microbial composition in infant stool were associated with a study definition of IgE-FA at 3-5 years of age. This included evidence of a lack of bacterial diversity, deficiencies in specific OTUs, and delayed microbial maturation. Results support dysbiosis in IgE-FA pathogenesis.

Public Health Sciences

Leonard-Murali S, **Ivanics T**, **Kwon DS**, **Han X**, **Steffes CP**, and **Shah R**. Local resection versus radical surgery for parathyroid carcinoma: A National Cancer Database analysis. *Eur J Surg Oncol* 2021; 47(11):2768-2773. PMID: 34229923. Full Text

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INTRODUCTION: Parathyroid carcinoma (PC) is rare and often diagnosed incidentally after local resection (LR) for other indications. Although recommended treatment has traditionally been radical surgery (RS), more recent guidelines suggest that LR alone may be adequate. We sought to further investigate outcomes of RS versus LR for localized PC. MATERIALS AND METHODS: PC patients from 2004 to 2015 with localized disease were identified from the National Cancer Database, then stratified by surgical therapy: LR or RS. Demographic and clinicopathologic data were compared. Cox proportional hazard models were constructed to estimate associations of variables with overall survival (OS). OS was estimated from time of diagnosis using Kaplan-Meier curves. RESULTS: A total of 555 patients were included (LR = 522, RS = 33). The groups were comparable aside from LR patients having higher rates of unknown nodal status (66.9% versus 39.4%; p = 0.003). By multivariable analysis, RS did not have a significant association with OS (hazard ratio (HR) = 0.43, 95% confidence interval (95%CI) = 0.10, 1.83; p = 0.255), nor did positive nodal status (HR = 0.66, 95%CI = 0.09, 5.03; p = 0.692) and unknown nodal status (HR = 1.30, 95%CI = 0.78, 2.17; p = 0.311). There was no difference in OS between the LR and RS groups, with median survival not reached by either group at 10 years (median follow-up = 60.4 months; p = 0.20). CONCLUSIONS: There was no difference in OS between LR and RS for localized PC. RS and nodal status may not impact survival as previously identified, and LR should remain a valid initial surgical approach. Future higher-powered studies are necessary to assess the effects of surgical approaches on morbidity and oncologic outcomes.

Public Health Sciences

Li P, Zhao W, **Kaatz S**, **Latack K**, **Schultz L**, and **Poisson L**. Factors Associated With Risk of Postdischarge Thrombosis in Patients With COVID-19. *JAMA Netw Open* 2021; 4(11). PMID: 34807256. Full Text

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IMPORTANCE: COVID-19 is associated with a high incidence of thrombotic events; however, the need for extended thromboprophylaxis after hospitalization remains unclear. OBJECTIVE: To quantify the rate of postdischarge arterial and venous thromboembolism in patients with COVID-19, identify the factors associated with the risk of postdischarge venous thromboembolism, and evaluate the association of postdischarge anticoagulation use with venous thromboembolism incidence. DESIGN, SETTING, AND PARTICIPANTS: This is a cohort study of adult patients hospitalized with COVID-19 confirmed by a positive SARS-CoV-2 test. Eligible patients were enrolled at 5 hospitals of the Henry Ford Health System from March 1 to November 30, 2020. Data analysis was performed from April to June 2021. EXPOSURES: Anticoagulant therapy after discharge. MAIN OUTCOMES AND MEASURES: New onset of symptomatic arterial and venous thromboembolic events within 90 days after discharge from the index admission for COVID-19 infection were identified using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes. RESULTS: In this cohort study of 2832 adult patients hospitalized with COVID-19, the mean (SD) age was 63.4 (16.7) years (IQR, 53-75 years), and 1347 patients (47.6%) were men. Thirty-six patients (1.3%) had postdischarge venous thromboembolic events (16 pulmonary embolism, 18 deep vein thrombosis, and 2 portal vein thrombosis). Fifteen (0.5%) postdischarge arterial thromboembolic events were observed (1 transient ischemic attack and 14 acute coronary syndrome). The risk of venous thromboembolism decreased with time (Mann-Kendall trend test, $P < .001$), with a median (IQR) time to event of 16 (7-43) days. There was no change in the risk of arterial thromboembolism with time (Mann-Kendall trend test, $P = .37$), with a median (IQR) time to event of 37 (10-63) days. Patients with a history of venous thromboembolism (odds ratio [OR], 3.24; 95% CI, 1.34-7.86), peak dimerized plasmin fragment D (D-dimer) level greater than 3 µg/mL (OR, 3.76; 95% CI, 1.86-7.57), and predischarge C-reactive protein level greater than 10 mg/dL (OR, 3.02; 95% CI, 1.45-6.29) were more likely to experience venous thromboembolism after discharge. Prescriptions for therapeutic anticoagulation at discharge were associated with reduced incidence of venous thromboembolism (OR, 0.18; 95% CI, 0.04-0.75; $P = .02$). CONCLUSIONS AND RELEVANCE: Although extended thromboprophylaxis in unselected patients with COVID-19 is not supported, these findings suggest that postdischarge anticoagulation may be considered for high-risk patients who have a history of venous thromboembolism, peak D-dimer level greater than 3 µg/mL, and predischarge C-reactive protein level greater than 10 mg/dL, if their bleeding risk is low.

Public Health Sciences

Nassiri F, Wang JZ, Au K, Barnholtz-Sloan J, Jenkinson MD, Drummond K, **Zhou Y**, **Snyder JM**, Brastianos P, Santarius T, Suppiah S, **Poisson L**, Gaillard F, Rosenthal M, Kaufmann T, Tsang D, Aldape K, and Zadeh G. Consensus core clinical data elements for meningiomas. *Neuro Oncol* 2021; Epub ahead of print. PMID: 34791428. Full Text

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BACKGROUND: With increasing molecular analyses of meningiomas, there is a need to harmonize language used to capture clinical data across centers to ensure that molecular alterations are appropriately linked to clinical variables of interest. Here the International Consortium on Meningiomas presents a set of core and supplemental meningioma-specific Common Data Elements (CDEs) to

facilitate comparative and pooled analyses. METHODS: The generation of CDEs followed the four-phase process similar to other National Institute of Neurological Disorders and Stroke (NINDS) CDE projects: discovery, internal validation, external validation, and distribution. RESULTS: The CDEs were organized into patient- and tumor-level modules. In total, 17 core CDEs (10 patient-level and 7-tumour-level) as well as 14 supplemental CDEs (7 patient-level and 7 tumour-level) were defined and described. These CDEs are now made publicly available for dissemination and adoption. CONCLUSIONS: CDEs provide a framework for discussion in the neuro-oncology community that will facilitate data sharing for collaborative research projects and aid in developing a common language for comparative and pooled analyses. The meningioma-specific CDEs presented here are intended to be dynamic parameters that evolve with time and The Consortium welcomes international feedback for further refinement and implementation of these CDEs.

Public Health Sciences

Smith-Bindman R, Yu S, Wang Y, Kohli MD, Chu P, Chung R, Luong J, Bos D, Stewart C, Bista B, Alejandrez Cisneros A, Delman B, Einstein AJ, **Flynn M**, Romano P, Seibert JA, Westphalen AC, and Bindman A. An Image Quality-informed Framework for CT Characterization. *Radiology* 2021; Epub ahead of print. PMID: 34751618. Full Text

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Background Lack of standardization in CT protocol choice contributes to radiation dose variation. Purpose To create a framework to assess radiation doses within broad CT categories defined according to body region and clinical imaging indication and to cluster indications according to the dose required for sufficient image quality. Materials and Methods This was a retrospective study using Digital Imaging and Communications in Medicine metadata. CT examinations in adults from January 1, 2016 to December 31, 2019 from the University of California San Francisco International CT Dose Registry were grouped into 19 categories according to body region and required radiation dose levels. Five body regions had a single dose range (ie, extremities, neck, thoracolumbar spine, combined chest and abdomen, and combined thoracolumbar spine). Five additional regions were subdivided according to dose. Head, chest, cardiac, and abdomen each had low, routine, and high dose categories; combined head and neck had routine and high dose categories. For each category, the median and 75th percentile (ie, diagnostic reference level [DRL]) were determined for dose-length product, and the variation in dose within categories versus across categories was calculated and compared using an analysis of variance. Relative median and DRL (95% CI) doses comparing high dose versus low dose categories were calculated. Results Among 4.5 million examinations, the median and DRL doses varied approximately 10 times between categories compared with between indications within categories. For head, chest, abdomen, and cardiac (3 266 546 examinations [72%]), the relative median doses were higher in examinations assigned to the high dose categories than in examinations assigned to the low dose categories, suggesting the assignment of indications to the broad categories is valid (head, 3.4-fold higher [95% CI: 3.4, 3.5]; chest, 9.6 [95% CI: 9.3, 10.0]; abdomen, 2.4 [95% CI: 2.4, 2.5]; and cardiac, 18.1 [95% CI: 17.7, 18.6]). Results were similar for DRL doses (all $P < .001$). Conclusion Broad categories based on image quality requirements are a

suitable framework for simplifying radiation dose assessment, according to expected variation between and within categories. © RSNA, 2021 See also the editorial by Mahesh in this issue.

Pulmonary and Critical Care Medicine

Axfors C, Janiaud P, Schmitt AM, Van't Hooft J, Smith ER, Haber NA, Abayomi A, Abduljalil M, Abdulrahman A, Acosta-Ampudia Y, Aguilar-Guisado M, Al-Beidh F, Alejandria MM, Alfonso RN, Ali M, AlQahtani M, AlZamrooni A, Anaya JM, Ang MAC, Aomar IF, Argumanis LE, Averyanov A, Baklaushev VP, Balionis O, Benfield T, Berry S, Birocco N, Bonifacio LB, Bowen AC, Bown A, Cabello-Gutierrez C, Camacho B, Camacho-Ortiz A, Campbell-Lee S, **Cao DH**, Cardesa A, Carnate JM, Castillo GJJ, Cavallo R, Chowdhury FR, Chowdhury FUH, Ciccone G, Cingolani A, Climacosa FMM, Compernolle V, Cortez CFN, Costa Neto A, D'Antico S, Daly J, Danielle F, Davis JS, De Rosa FG, Denholm JT, Denkinger CM, Desmecht D, Díaz-Coronado JC, Díaz Ponce-Medrano JA, Donneau AF, Dumagay TE, Dunachie S, Dungog CC, Erinoso O, Escasa IMS, Estcourt LJ, Evans A, Evasan ALM, Fareli CJ, Fernandez-Sanchez V, Galassi C, Gallo JE, Garcia PJ, Garcia PL, Garcia JA, Garigliany M, Garza-Gonzalez E, Gauiran DTV, Gaviria García PA, Giron-Gonzalez JA, Gómez-Almaguer D, Gordon AC, Gothot A, Grass Guaqueta JS, Green C, Grimaldi D, Hammond NE, Harvala H, Heralde FM, Herrick J, Higgins AM, Hills TE, **Hines J**, Holm K, Hoque A, Hoste E, Ignacio JM, Ivanov AV, Janssen M, **Jennings JH**, Jha V, King RAN, Kjeldsen-Kragh J, Klenerman P, **Kotecha A**, Krapp F, Labanca L, Laing E, Landin-Olsson M, Laterre PF, Lim LL, Lim J, Ljungquist O, Llaca-Díaz JM, López-Robles C, López-Cárdenas S, Lopez-Plaza I, Lucero JAC, Lundgren M, Macías J, Maganito SC, Malundo AFG, Manrique RD, Manzini PM, Marcos M, Marquez I, Martínez-Marcos FJ, Mata AM, McArthur CJ, McQuilten ZK, McVerry BJ, Menon DK, Meyfroidt G, Mirasol MAL, Misset B, Molton JS, Mondragon AV, Monsalve DM, Moradi Choghakabodi P, Morpeth SC, Mouncey PR, Moutschen M, Müller-Tidow C, **Murphy E**, Najdovski T, Nichol AD, Nielsen H, Novak RM, O'Sullivan MVN, Olalla J, Osibogun A, Osikomaiya B, Oyonarte S, Pardo-Oviedo JM, Patel MC, Paterson DL, Peña-Perez CA, Perez-Calatayud AA, Pérez-Alba E, Perkina A, Perry N, Pouladzadeh M, Poyato I, Price DJ, Quero AKH, Rahman MM, Rahman MS, **Ramesh M**, Ramírez-Santana C, Rasmussen M, Rees MA, Rego E, Roberts JA, Roberts DJ, Rodríguez Y, Rodríguez-Baño J, Rogers BA, Rojas M, Romero A, Rowan KM, Saccona F, Safdarian M, Santos MCM, Sasadeusz J, Scozzari G, Shankar-Hari M, **Sharma G**, Snelling T, Soto A, Tagayuna PY, **Tang A**, **Tatem G**, Teofili L, Tong SYC, Turgeon AF, Veloso JD, Venkatesh B, Ventura-Enriquez Y, Webb SA, Wiese L, Wikén C, Wood EM, Yusubalieva GM, Zacharowski K, Zarychanski R, Khanna N, Moher D, Goodman SN, Ioannidis JPA, and Hemkens LG. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis* 2021; 21(1):1170. PMID: 34800996. Full Text

BACKGROUND: Convalescent plasma has been widely used to treat COVID-19 and is under investigation in numerous randomized clinical trials, but results are publicly available only for a small number of trials. The objective of this study was to assess the benefits of convalescent plasma treatment compared to placebo or no treatment and all-cause mortality in patients with COVID-19, using data from all available randomized clinical trials, including unpublished and ongoing trials (Open Science Framework, https://doi.org/10.17605/OSF.IO/GEHFX). METHODS: In this collaborative systematic review and meta-analysis, clinical trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform), the Cochrane COVID-19 register, the LOVE database, and PubMed were searched until April 8, 2021. Investigators of trials registered by March 1, 2021, without published results were contacted via email. Eligible were ongoing, discontinued and completed randomized clinical trials that compared convalescent plasma with placebo or no treatment in COVID-19 patients, regardless of setting or treatment schedule. Aggregated mortality data were extracted from publications or provided by investigators of unpublished trials and combined using the Hartung-Knapp-Sidik-Jonkman random effects model. We investigated the contribution of unpublished trials to the overall evidence. RESULTS: A total of 16,477 patients were included in 33 trials (20 unpublished with 3190 patients, 13 published with 13,287 patients). 32 trials enrolled only hospitalized patients (including 3 with only intensive care unit patients). Risk of bias was low for 29/33 trials. Of 8495 patients who received convalescent plasma, 1997 died (23%), and of 7982 control patients, 1952 died (24%). The combined risk ratio for all-cause mortality was 0.97 (95% confidence interval: 0.92; 1.02) with between-study heterogeneity not beyond chance ($I(2) = 0\%$). The RECOVERY trial had 69.8% and the unpublished evidence 25.3% of the weight in the meta-analysis. CONCLUSIONS: Convalescent plasma treatment of patients with COVID-19 did not

reduce all-cause mortality. These results provide strong evidence that convalescent plasma treatment for patients with COVID-19 should not be used outside of randomized trials. Evidence synthesis from collaborations among trial investigators can inform both evidence generation and evidence application in patient care.

Pulmonary and Critical Care Medicine

Chupp G, Kline JN, Khatri SB, McEvoy C, Silvestri GA, Shifren A, Castro M, Bansal S, McClelland M, Dransfield M, Trevor J, Kahlstrom N, **Simoff M**, Wahidi MM, Lamb CR, Ferguson JS, Haas A, Hogarth DK, Tejedor R, Toth J, Hey J, Majid A, LaCamera P, FitzGerald JM, Enfield K, Grubb GM, McMullen EA, Olson JL, and Laviolette M. Bronchial Thermoplasty in Severe Asthmatics At 5 Years: The PAS2 Study. *Chest* 2021; Epub ahead of print. PMID: 34774528. Full Text

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Lahey Hospital and Medical Center - Burlington, MA/US.
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University of Chicago - Chicago, IL/US.
LSU Health Science Center - New Orleans, LA/US.
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St. Elizabeth's Medical Center of Boston, Inc. - Boston, MA/US.
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University of Virginia Health System - Charlottesville, VA/US.
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BACKGROUND: Bronchial thermoplasty is a device-based treatment for subjects ≥18 years with severe asthma poorly controlled with inhaled corticosteroids and long-acting beta-agonists. The Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma (PAS2) study collected data on severe asthmatics undergoing this procedure. RESEARCH QUESTION: What are the 5-year efficacy and safety results in severe asthmatics who have undergone bronchial thermoplasty? STUDY DESIGN AND METHODS: This was a prospective, open-label, observational, multi-center study conducted in the United States and Canada. Subjects aged 18-65, taking inhaled corticosteroids ≥1000µg/day (beclomethasone or equivalent) and long-acting β-agonists ≥80µg/day (salmeterol or equivalent) were included. Severe exacerbations, hospitalization, emergency department visits, and medication usage were evaluated for the 12 months prior to and at years 1-5 post-treatment. Spirometry was evaluated at baseline and at years 1-5 post-treatment. RESULTS: 284 subjects were enrolled at 27 centers; 227 subjects (80%) completed 5 years of follow-up. By year 5 post-treatment, the proportion of subjects with severe exacerbations, emergency department visits, and hospitalizations was 42.7%, 7.9%, and 4.8%, respectively, compared to 77.8%, 29.4%, and 16.1% in the 12 months prior to treatment. The proportion of subjects on maintenance oral corticosteroids decreased from 19.4% at baseline to 9.7% at 5 years. Analyses of subgroups based on baseline clinical and biomarker characteristics revealed a statistically significant clinical improvement among all subgroups. INTERPRETATION: Five years after

treatment, subjects experienced decreases in severe exacerbations, hospitalizations, emergency department visits and corticosteroid exposure. All subgroups demonstrated clinically significant improvement, suggesting that bronchial thermoplasty improves asthma control in different asthma phenotypes.

Pulmonary and Critical Care Medicine

Diaz-Mendoza J, Celis Valdiviezo E, Patel NM, and **Simoff MJ**. One-session bilateral sequential whole lung lavage (OSBSWLL) for the management of pulmonary alveolar proteinosis. *BMC Pulm Med* 2021; 21(1):358. PMID: 34749694. Full Text

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BACKGROUND: Whole Lung Lavage (WLL) has been an important part in the management of Pulmonary Alveolar Proteinosis (PAP) since it improves radiologic and clinical parameters. Bilateral WLL is usually performed in two sessions on different days. Few case reports have described one-session bilateral sequential lung lavage (OSBSWLL), and none have described ambulatory management (same-day discharge). METHODS: Demographic characteristics, physiologic parameters, procedure details and outcomes were retrospectively collected on consecutive patients who underwent OSBSWLL for PAP following an ambulatory protocol stablished in our institution. RESULTS: A total of 13 patients underwent 30 OSBSWLL (61.5% male; mean age 40). The mean SpO2 was 90% (IQR 9) and 94% (IQR 6), before and after OSBSWLL respectively. In 63.3% of cases, patients were discharged home the same day of procedure. Only in two cases (6.6%), patients required post-procedure prolonged mechanical ventilation (> 4 h) due to persistent hypoxia. CONCLUSIONS: OSBSWLL can be performed with same-day discharge.

Radiation Oncology

Bagher Ebadian H, **Siddiqui F**, **Ghanem A**, **Zhu S**, **Lu M**, **Movsas B**, and **Chetty IJ**. Radiomics outperforms clinical factors in characterizing human papilloma virus (HPV) for patients with oropharyngeal squamous cell carcinomas. *Biomed Phys Eng Express* 2021; Epub ahead of print. PMID: 34781281. Full Text

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Purpose:To utilize radiomic features extracted from CT images to characterize Human Papilloma Virus (HPV) for patients with oropharyngeal cancer squamous cell carcinoma (OPSCC).Methods:One hundred twenty-eight OPSCC patients with known HPV-status (60-HPV+ and 68-HPV-, confirmed by immunohistochemistry-P16-protein testing) were retrospectively studied. Radiomic features (11 feature-categories) were extracted in 3D from contrast-enhanced (CE)-CT images of gross-tumor-volumes using 'in-house' software ('ROdiomiX') developed and validated following the image-biomarker-standardization-initiative (IBSI) guidelines. Six clinical factors were investigated: Age-at-Diagnosis, Gender, Total-

Charlson, Alcohol-Use, Smoking-History, and T-Stage. A Least-Absolute-Shrinkage-and-Selection-Operation (Lasso) technique combined with a Generalized-Linear-Model (Lasso-GLM) were applied to perform regularization in the radiomic and clinical feature spaces to identify the ranking of optimal feature subsets with most representative information for prediction of HPV. Lasso-GLM models/classifiers based on clinical factors only, radiomics only, and combined clinical and radiomics (ensemble/integrated) were constructed using random-permutation-sampling. Tests of significance (One-way ANOVA), average Area-Under-Receiver-Operating-Characteristic (AUC), and Positive and Negative Predictive values (PPV and NPV) were computed to estimate the generalization-error and prediction performance of the classifiers.Results:Five clinical factors, including T-stage, smoking status, and age, and 14 radiomic features, including tumor morphology, and intensity contrast were found to be statistically significant discriminators between HPV positive and negative cohorts. Performances for prediction of HPV for the 3 classifiers were: Radiomics-Lasso-GLM: AUC/PPV/NPV=0.789/0.755/0.805; Clinical-Lasso-GLM: 0.676/0.747/0.672, and Integrated/Ensemble-Lasso-GLM: 0.895/0.874/0.844. Results imply that the radiomics-based classifier enabled better characterization and performance prediction of HPV relative to clinical factors, and that the combination of both radiomics and clinical factors yields even higher accuracy characterization and predictive performance.Conclusion:Albeit subject to confirmation in a larger cohort, this pilot study presents encouraging results in support of the role of radiomic features towards characterization of HPV in patients with OPSCC.

Radiation Oncology

Cook A, Modh A, **Ali H**, **Sheqwara J**, **Chang S**, **Ghanem T**, **Momin S**, **Wu V**, **Tam S**, **Money S**, **Han X**, **Fakhoury L**, **Movsas B**, and **Siddiqui F**. Randomized Phase III, Double Blind, Placebo-Controlled Study of Prophylactic Gabapentin for the Reduction of Oral Mucositis Pain During the Treatment of Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; Epub ahead of print. PMID: 34808255. Full Text

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PURPOSE: To determine if prophylactic gabapentin usage in patients undergoing definitive concurrent chemoradiotherapy (chemoRT) for oropharyngeal cancer (OPC) improves treatment-related oral mucositis pain, opioid use, and feeding tube (FT) placement. METHODS AND MATERIALS: This double-blind, randomized phase III study for patients with locally advanced OPC undergoing chemoRT randomly allocated patients to prophylactic gabapentin (600 mg thrice daily) or placebo. The primary endpoint was change in Patient-Reported Oral Mucositis Symptom (PROMS) scores over the entire treatment period (baseline to 6 weeks post-RT follow-up) with higher scores indicating worse outcomes. Opioid requirements, FT placement, and other patient-reported QOL metrics (Functional Assessment of Cancer Therapy-Head and Neck [FACT-HN] and Patient-Reported Outcomes of Common Terminology Criteria for Adverse Events [PRO-CTCAE]) were assessed. Lower scores suggested poorer quality of life (QOL) with the FACT-HN questionnaire, and higher scores suggested worse outcomes with the PRO-CTCAE questionnaire. Questionnaires were administered at baseline, weekly during RT, and at 6-week post-RT follow-up. Repeated measures analysis of variance were used to detect differences in PROMS scores and change in opioid use from baseline. Wilcoxon-rank sum tests were used to compare averages for the other secondary endpoints. A p-value less than .05 was considered statistically significant. RESULTS: Treatment arms were well-balanced overall, including T and N staging and dosimetric variables. There were 58 patients analyzed. No significant difference was found in PROMS scores (mean 29.1, Standard Deviation [SD] 22.5, vs 20.1, SD 16.8, for gabapentin vs placebo, respectively, p = .11). The FACT-HN functional well-being index had a significant decrease in scores from baseline to follow-up in the gabapentin arm (median -6, interquartile range [IQR] -10.0 to -0.5, vs -1, IQR -5.5 to 3.0, p = .03). PRO-

CTCAE scores increased significantly at follow-up for gabapentin (median 6.5, IQR 3.5 to 11.8, vs 1, IQR -2.0 to 6.0, p = .01). There was no significant difference in average or change in opioid use. FT placement was significantly higher in the gabapentin arm (62.1% vs 20.7%, p < .01). CONCLUSIONS: This study suggests that prophylactic gabapentin is not effective in improving treatment-related oral mucositis symptoms in a select population of patients with OPC undergoing definitive chemoRT.

Radiation Oncology
Hathout L, **Elshaikh MA**, and Albuquerque KV. In reply to Onal et al. *Int J Radiat Oncol Biol Phys* 2021; 111(3):838-839. PMID: 34560029. Full Text

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Radiation Oncology
Wilkie JR, Hochstedler KA, Schipper MJ, Matuszak MM, Paximadis P, Dominello MM, Grills I, Hayman JA, Dess R, Dragovic AF, Jagsi R, Pierce LJ, Spratt DE, Bergsma D, Boike TP, **Movsas B**, and Jolly S. Association Between Physician and Patient Reported Symptoms in Patients Treated with Definitive Radiotherapy for Locally Advanced Lung Cancer in a Statewide Consortium. *Int J Radiat Oncol Biol Phys* 2021; Epub ahead of print. PMID: 34838865. Full Text

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INTRODUCTION: Little data have been reported about the patient experience during curative radiotherapy for lung cancer in routine clinical practice, or how this relates to treatment toxicity reported by clinicians. The purpose of this study was to compare clinician-reported adverse events (AEs) with patient-reported outcomes (PROs) including both specific symptoms/side effects as well as overall quality of life (QOL) during and after definitive radiotherapy (RT) for locally advanced lung cancer (LALC) in a large statewide cohort. METHODS AND MATERIALS: Patient-reported outcomes (PROs) were prospectively collected from patients treated with definitive radiotherapy for LALC at 24 institutions within the XXXX Radiation Oncology Quality Consortium between 2012-2018 using the Functional Assessment of Cancer Therapy Trial Outcome Index (FACT-TOI). Physicians prospectively recorded adverse events (AEs) using CTCAE version 4.0. Patient-reported quality of life (QOL) changes from baseline were assessed during and after radiotherapy using the FACT-TOI. Spearman correlation coefficients were calculated for AEs and similar PROs, and multivariable analysis was used to assess associations with QOL. RESULTS: 1361 patients were included and 53% of respondents reported clinically meaningful declines in QOL at the end of RT. Correlation between clinician-reported esophagitis and patient-reported trouble swallowing was moderate (R=0.67) while correlations between clinician-reported pneumonitis and patient-reported shortness of breath (R=0.13) and cough (R=0.09) were weak. Clinician-reported AEs were significantly associated with clinically meaningful declines inpatient-reported QOL, with R=-0.46 for a summary AE-score. QOL was more strongly associated with fatigue (R=-0.41) than lung-specific AEs. CONCLUSIONS: AEs are associated with clinically meaningful declines in QOL during and after RT for

LALC, but associations between AEs and QOL are only modest. This highlights the importance of PRO data, and future research should assess whether earlier detection of PRO changes could allow for interventions that reduce the frequency of treatment-related clinically meaningful declines in QOL.

Radiation Oncology

Yoon J, Fitzgerald H, Wang Y, Wang Q, Vergalasova I, **Elshaikh MA**, **Dimitrova I**, Damast S, Li JY, Fields EC, Beriwal S, Keller A, Kidd EA, Usoz M, Jolly S, Jaworski E, Leung EW, Donovan E, Taunk NK, Chino J, Natesan D, Russo AL, Lea JS, Albuquerque KV, Lee LJ, and Hathout L. Does prophylactic para-aortic lymphatic irradiation improve outcomes in women with stage IIIC1 endometrial carcinoma? A multi-institutional pooled analysis. *Pract Radiat Oncol* 2021; Epub ahead of print. PMID: 34822999. Full Text

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PURPOSE: To evaluate the impact of prophylactic PALN RT on clinical outcomes in patients with FIGO 2018 stage IIIC1 EC. MATERIALS/METHODS: A multi-institutional retrospective study included patients with FIGO 2018 stage IIIC1 EC status post surgical staging, lymph node assessment followed by adjuvant chemotherapy and radiotherapy using various sequencing regimens. Overall survival (OS) and recurrence-free survival (RFS) rates were estimated by Kaplan-Meier method. Univariable and multivariable analysis were performed by Cox proportional hazard models for RFS/OS. In addition, propensity score matching were used to estimate the effect of the radiation field extent on survival outcomes. RESULTS: A total of 378 patients were included with a median follow-up of 45.8 months. Pelvic RT was delivered to 286 patients while 92 patients received pelvic and PALN RT. The estimated OS and RFS rates at 5 years for the entire cohort were 80% and 69%, respectively. There was no difference in the 5-year OS (77% vs. 87%, p=0.47) and RFS rates (67% vs. 70%, p=0.78) between patients treated with pelvic RT and those with pelvic and prophylactic PALN RT, respectively. After propensity score matching, the estimated Hazard Ratios (HR) of prophylactic PALN RT vs. pelvic RT were 1.50 (95% CI = (0.71, 3.19), p-value = 0.28) for OS and 1.24 (95% CI = (0.64, 2.42), p-value = 0.51) for RFS suggesting that prophylactic PALN RT does not improve survival outcomes. Distant recurrence was the most common site of first recurrence, and the extent of RT field was not associated with the site of first recurrence (P=0.79). CONCLUSIONS: Prophylactic PALN RT was not significantly associated with improved survival outcomes in stage IIIC1 EC. Distant metastases remain the most site of failure despite routine use of systemic chemotherapy, new therapeutic approaches are necessary to optimize the outcomes for women with stage IIIC1 EC.

Research Administration

Akhavan S, and **Soltanian-Zadeh H**. Blind separation of sparse sources from nonlinear mixtures. *Digital Signal Processing* 2021; 118. PMID: 10.1016/j.dsp.2021.103220. Request Article

Research Administration

Elisevich K, **Davoodi-Bojd E**, Heredia JG, and **Soltanian-Zadeh H**. Prospective Quantitative Neuroimaging Analysis of Putative Temporal Lobe Epilepsy. *Front Neurol* 2021; 12:747580. PMID: 34803885. Full Text

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Purpose: A prospective study of individual and combined quantitative imaging applications for lateralizing epileptogenicity was performed in a cohort of consecutive patients with a putative diagnosis of mesial temporal lobe epilepsy (mTLE). Methods: Quantitative metrics were applied to MRI and nuclear medicine imaging studies as part of a comprehensive presurgical investigation. The neuroimaging analytics were conducted remotely to remove bias. All quantitative lateralizing tools were trained using a separate dataset. Outcomes were determined after 2 years. Of those treated, some underwent resection, and others were implanted with a responsive neurostimulation (RNS) device. Results: Forty-eight consecutive cases underwent evaluation using nine attributes of individual or combinations of neuroimaging modalities: 1) hippocampal volume, 2) FLAIR signal, 3) PET profile, 4) multistructural analysis (MSA), 5) multimodal model analysis (MMM), 6) DTI uncertainty analysis, 7) DTI connectivity, and 9) fMRI connectivity. Of the 24 patients undergoing resection, MSA, MMM, and PET proved most effective in predicting an Engel class 1 outcome (>80% accuracy). Both hippocampal volume and FLAIR signal analysis showed 76% and 69% concordance with an Engel class 1 outcome, respectively. Conclusion: Quantitative multimodal neuroimaging in the context of a putative mTLE aids in declaring laterality. The degree to which there is disagreement among the various quantitative neuroimaging metrics will judge whether epileptogenicity can be confined sufficiently to a particular temporal lobe to warrant further study and choice of therapy. Prediction models will improve with continued exploration of combined optimal neuroimaging metrics.

Sleep Medicine

Cheng P, Casement MD, Cuellar R, Johnson DA, **Kalmbach D**, **Cuamatzi Castelan A**, and **Drake CL**. Sleepless in COVID-19: racial disparities during the pandemic as a consequence of structural inequity. *Sleep* 2021; Epub ahead of print. PMID: 34788453. Full Text

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STUDY OBJECTIVES: Insomnia has been on the rise during the 2019 coronavirus disease (COVID-19) pandemic, which may disproportionately affect racial minorities. This study characterized racial disparities in insomnia during the pandemic and evaluated mechanisms for such disparities. METHODS: Participants included 196 adults (48 Black) from a 2016-2017 clinical trial of insomnia treatment who were reevaluated in April 2020. Race was evaluated as a predictor of change in insomnia, impact of COVID-19, and COVID-19 stress. Mediation models using the PRODCLIN method evaluated the extent to which: (1) COVID-19 impact accounted for Black-White disparities in change in insomnia, and (2) COVID-19 stress accounted for associations between discrimination and change in insomnia. RESULTS: Increases in insomnia symptoms during COVID-19 were greater in Black compared to White participants, with 4.3 times the odds of severe insomnia (Insomnia Severity Index ≥ 22). Symptom severity was associated with pre-pandemic experiences of discrimination. Black participants were also disproportionately impacted by COVID-19, with twice the odds of irreparable loss of income/employment and four times the rate of COVID-19 diagnoses in their sociofamilial network compared to White participants. The disproportionate impact of COVID-19 accounted for 69.2% of the relationship between race and change in insomnia

severity, and COVID-19 related stress accounted for 66.5% of the relationship between prior history of racial discrimination and change in insomnia severity. CONCLUSIONS: Black-White disparities in insomnia severity during COVID-19 may be driven by structural inequities resulting in the disproportionate impact of COVID-19 on Black Americans. Results lend support for the minority stress model in the context of sleep health. CLINICAL TRIAL REGISTRATION: Sleep to Prevent Evolving Affecting Disorders (SPREAD). NCT number: NCT02988375. https://clinicaltrials.gov/ct2/show/NCT02988375.

Sleep Medicine

Gurubhagavatula I, Barger LK, Barnes CM, Basner M, Boivin DB, Dawson D, **Drake CL**, Flynn-Evans EE, Mysliwiec V, Patterson PD, Reid KJ, Samuels C, Shattuck NL, Kazmi U, Carandang G, Heald JL, and Van Dongen HPA. Guiding principles for determining work shift duration and addressing the effects of work shift duration on performance, safety, and health: guidance from the American Academy of Sleep Medicine and the Sleep Research Society. *J Clin Sleep Med* 2021; 17(11):2283-2306. PMID: 34666885. Full Text

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Risks associated with fatigue that accumulates during work shifts have historically been managed through working time arrangements that specify fixed maximum durations of work shifts and minimum durations of time off. By themselves, such arrangements are not sufficient to curb risks to performance, safety, and health caused by misalignment between work schedules and the biological regulation of waking alertness and sleep. Science-based approaches for determining shift duration and mitigating associated risks, while addressing operational needs, require: (1) a recognition of the factors contributing to fatigue and fatigue-related risks; (2) an understanding of evidence-based countermeasures that may reduce fatigue and/or fatigue-related risks; and (3) an informed approach to selecting workplace-specific strategies for managing work hours. We propose a series of guiding principles to assist stakeholders with designing a shift duration decision-making process that effectively balances the need to meet operational demands with the need to manage fatigue-related risks.

Surgery

Chang DD, and Han JJ. The TransMedics Organ Care System for the Liver receives FDA pre-market approval. *Artif Organs* 2021; Epub ahead of print. PMID: 34802155. Full Text

The Federal Drug Administration grants pre-market approval to TransMedics Organ Care System Liver, a platform designed to prolong donor organ viability via ex vivo perfusion in preparation for transplant.

Surgery

Fayed M, **Patel N**, **Yeldo N**, **Nowak K**, **Penning DH**, **Vasconcelos Torres F**, **Natour AK**, and **Chhina A**. Effect of Intubation Timing on the Outcome of Patients With Severe Respiratory Distress Secondary to COVID-19 Pneumonia. *Cureus* 2021; 13(11). PMID: 34804753. Full Text

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Background The optimal timing of intubation for critically ill patients with severe respiratory illness remains controversial among healthcare providers. The coronavirus disease 2019 (COVID-19) pandemic has raised even more questions about when to implement this life-saving therapy. While one group of providers prefers early intubation for patients with respiratory distress because these patients may deteriorate rapidly without it, other providers believe that intubation should be delayed or avoided because of its associated risks including worse outcomes. Research question Our objective was to assess whether the timing of intubation in patients with severe COVID-19 pneumonia was associated with differences in mortality or other outcomes. Study design and methods This was a single-center retrospective observational cohort study. We analyzed outcomes of patients who were intubated secondary to COVID-19 pneumonia between March 13, 2020, and December 12, 2020, at Henry Ford Hospital in Detroit, Michigan. Patients were categorized into two groups: early intubated (intubated within 24 hours of the onset of severe respiratory distress) and late intubated (intubated after 24 hours of the onset of severe respiratory distress). Demographics, comorbidities, respiratory rate oxygenation (ROX) index, sequential organ failure assessment (SOFA) score, and treatment received were compared between groups. The primary outcome was mortality. Secondary outcomes were ventilation time, intensive care unit stay, hospital length of stay, and discharge disposition. Post hoc and Kaplan-Meier survival analyses were performed. Results A total of 110 patients were included: 55 early intubated and 55 late intubated. We did not observe a significant difference in overall mortality between the early intubated (43%) and the late intubated groups (53%) ($p = 0.34$). There was no statistically significant difference in patients' baseline characteristics including SOFA scores (the early intubation group had a mean score of 7.5 compared to 6.7 in the late intubation group). Based on the ROX index, the early intubation group had significantly more patients with a reduced risk of intubation (45%) than the late group (27%) ($p = 0.029$). The early intubation group was treated with a high-flow nasal cannula at a significantly lower rate (47%) than the late intubation group (83%) ($p < 0.001$). Significant differences in patient baseline characteristics, treatment received, and other outcomes were not observed. Post hoc analysis adjusting for SOFA score between 0 and 9 revealed significantly higher mortality in the late intubation group (49%) than in the early intubation group (26%) ($p = 0.03$). Patients in the 0 to 9 SOFA group who were intubated later had 2.7 times the odds of dying during hospital admission compared to patients who were intubated early (CI, 1.09-6.67). Interpretation The timing of intubation for patients with severe COVID-19 pneumonia was not significantly associated with overall mortality or other patient outcomes. However, within the subgroup of patients with SOFA scores of 9 or lower at the time of intubation, patients intubated after 24 hours of the onset of respiratory distress had a higher risk of death than those who were intubated within 24 hours of respiratory distress. Thus, patients with COVID-19 pneumonia who are not at a high level of organ dysfunction may benefit from early mechanical ventilation.

Surgery

Gupta K, **Viacava RC**, Jain V, Kakar TS, **Jesse M**, and Virani SS. Trends in Patient-Recalled Targets for Cardiovascular Risk Factors in Ambulatory US Adults With Diabetes Mellitus (from National Health and Nutrition Examination Survey). *Am J Cardiol* 2021; Epub ahead of print. PMID: 34839899. Full Text

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Surgery

Ivanics T, Claasen MP, Patel MS, Rajendran L, Shwaartz C, Raschzok N, Yoon P, Murillo Perez CF, Hansen BE, Muaddi H, Moulton CA, Reichman T, Ghanekar A, Gallinger S, McGilvray I, Cleary SP, and Sapisochin G. Long-term outcomes of laparoscopic liver resection for hepatocellular carcinoma: A propensity score matched analysis of a high-volume North American center. *Surgery* 2021; Epub ahead of print. PMID: 34742570. Full Text

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BACKGROUND: Laparoscopic liver resections for malignancy are increasing worldwide, and yet data from North America are lacking. We aimed to assess the long-term outcomes of patients undergoing laparoscopic liver resection and open liver resection as a treatment for hepatocellular carcinoma. METHODS: Patients undergoing liver resection for hepatocellular carcinoma between January 2008 and December 2019 were retrospectively studied. A propensity score matching was performed using patient demographics, laboratory parameters, etiology of liver disease, liver function, and tumor characteristics. Primary outcomes included overall survival and cumulative incidence of recurrence. Kaplan-Meier and competing risk cumulative incidence were used for survival analyses. Multivariable Cox regression and Fine-Gray proportional hazard regression were performed to determine hazard for death and recurrence, respectively. RESULTS: Three hundred and ninety-one patients were identified (laparoscopic liver resection: 110; open liver resection: 281). After propensity score matching, 149 patients remained (laparoscopic liver resection: 57; open liver resection: 92). There were no significant differences between groups with regard to extent of hepatectomy performed and tumor characteristics. The laparoscopic liver resection group experienced a lower proportion of ≥Clavien-Dindo grade III complications (14% vs 29%; P = .01). In the matched cohort, the 1-, 3-, and 5-year overall survival rate in the laparoscopic liver

resection versus open liver resection group was 90.9%, 79.3%, 70.5% vs 91.3%, 88.5%, 83.1% (P = .26), and the cumulative incidence of recurrence 31.1%, 59.7%, 62.9% vs 18.9%, 40.6%, 49.2% (P = .06), respectively. CONCLUSION: This study represents the largest single institutional study from North America comparing long-term oncologic outcomes of laparoscopic liver resection and open liver resection as a treatment for primary hepatocellular carcinoma. The combination of reduced short-term complications and equivalent long-term oncologic outcomes favor the laparoscopic approach when feasible.

Surgery
Ivanics T, Salinas-Miranda E, Abreu P, Khalvati F, **Namdar K**, **Dong X**, Deniffel D, Gorgen A, Erdman L, Jhaveri K, **Haider M**, Veit-Haibach P, and Sapisochin G. A Pre-TACE Radiomics Model to Predict HCC Progression and Recurrence in Liver Transplantation: A Pilot Study on a Novel Biomarker. *Transplantation* 2021; 105(11):2435-2444. PMID: 33982917. Full Text

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BACKGROUND: Despite transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC), a significant number of patients will develop progression on the liver transplant (LT) waiting list or disease recurrence post-LT. We sought to evaluate the feasibility of a pre-TACE radiomics model, an imaging-based tool to predict these adverse outcomes. METHODS: We analyzed the pre-TACE computed tomography images of patients waiting for a LT. The primary endpoint was a combined event that included waitlist dropout for tumor progression or tumor recurrence post-LT. The radiomic features were extracted from the largest HCC volume from the arterial and portal venous phase. A third set of features was created, combining the features from these 2 contrast phases. We applied a least absolute shrinkage and selection operator feature selection method and a support vector machine classifier. Three prognostic models were built using each feature set. The models' performance was compared using 5-fold cross-validated area under the receiver operating characteristic curves. RESULTS: . Eighty-eight patients were included, of whom 33 experienced the combined event (37.5%). The median time to dropout was 5.6 mo (interquartile range: 3.6-9.3), and the median time for post-LT recurrence was 19.2 mo (interquartile range: 6.1-34.0). Twenty-four patients (27.3%) dropped out and 64 (72.7%) patients were transplanted. Of these, 14 (21.9%) had recurrence post-LT. Model performance yielded a mean area under the receiver operating characteristic curves of 0.70 (±0.07), 0.87 (±0.06), and 0.81 (±0.06) for the arterial, venous, and the combined models, respectively. CONCLUSIONS: A pre-TACE radiomics model for HCC patients undergoing LT may be a useful tool for outcome prediction. Further external model validation with a larger sample size is required.

Surgery
Ivanics T, Wallace D, Abreu P, Claasen MP, Callaghan C, Cowling T, Walker K, Heaton N, Mehta N, Sapisochin G, and van der Meulen J. Survival After Liver Transplantation: An International Comparison Between the United States and the United Kingdom in the Years 2008-2016. *Transplantation* 2021; Epub ahead of print. PMID: 34753895. Full Text

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BACKGROUND: Compared with the United States, risk-adjusted mortality in the United Kingdom has historically been worse in the first 90 d following liver transplantation (LT) and better thereafter. In the last decade, there has been considerable change in the practice of LT internationally, but no contemporary large-scale international comparison of posttransplant outcomes has been conducted. This study aimed to determine disease-specific short- and long-term mortality of LT recipients in the United States and the United Kingdom. METHODS: This retrospective international multicenter cohort study analyzed adult (≥18 y) first-time LT recipients between January 2, 2008, and December 31, 2016, using the Organ Procurement and Transplantation Network/United Network for Organ Sharing and the UK Transplant Registry databases. Time-dependent Cox regression estimated hazard ratios (HRs) comparing disease-specific risk-adjusted mortality in the first 90 d post-LT, between 90 d and 1 y, and between 1 and 5 y. RESULTS: Forty-two thousand eight hundred seventy-four US and 4950 UK LT recipients were included. The main LT indications in the United States and the United Kingdom were hepatocellular carcinoma (25.4% and 24.9%, respectively) and alcohol-related liver disease (20.3% and 27.1%, respectively). There were no differences in mortality during the first 90 d post-LT (reference: United States; HR, 0.96; 95% confidence interval [CI], 0.82-1.12). However, between 90 d and 1 y (HR, 0.71; 95% CI, 0.59-0.85) and 1 and 5 y (HR, 0.71; 95% CI, 0.63-0.81]) the United Kingdom had lower mortality. The mortality differences between 1 and 5 y were most marked in hepatocellular carcinoma (HR, 0.71; 95% CI, 0.58-0.88) and alcohol-related liver disease patients (HR, 0.64; 95% CI, 0.45-0.89). CONCLUSIONS: Risk-adjusted mortality in the United States and the United Kingdom was similar in the first 90 d post-LT but better in the United Kingdom thereafter. International comparisons of LT may highlight differences in healthcare delivery and help benchmarking by identifying modifiable factors that can facilitate improved global outcomes in LT.

Surgery
Johanson H, and **Okereke I**. Commentary: A New Way to Gauge Pectus Severity. *Semin Thorac Cardiovasc Surg* 2021; Epub ahead of print. PMID: 34838955. Full Text

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Surgery
Johanson H, and **Okereke I**. The Importance of Clinical Decision-Making in Surgical Planning for Non-Small Cell Lung Cancer. *Ann Surg Oncol* 2021; Epub ahead of print. PMID: 34748123. Full Text

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Surgery
Leonard-Murali S, **Ivanics T**, **Kwon DS**, **Han X**, **Steffes CP**, and **Shah R**. Local resection versus radical surgery for parathyroid carcinoma: A National Cancer Database analysis. *Eur J Surg Oncol* 2021; 47(11):2768-2773. PMID: 34229923. Full Text

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INTRODUCTION: Parathyroid carcinoma (PC) is rare and often diagnosed incidentally after local resection (LR) for other indications. Although recommended treatment has traditionally been radical surgery (RS), more recent guidelines suggest that LR alone may be adequate. We sought to further investigate outcomes of RS versus LR for localized PC. MATERIALS AND METHODS: PC patients from 2004 to 2015 with localized disease were identified from the National Cancer Database, then stratified by surgical therapy: LR or RS. Demographic and clinicopathologic data were compared. Cox proportional hazard models were constructed to estimate associations of variables with overall survival (OS). OS was estimated from time of diagnosis using Kaplan-Meier curves. RESULTS: A total of 555 patients were included (LR = 522, RS = 33). The groups were comparable aside from LR patients having higher rates of unknown nodal status (66.9% versus 39.4%; p = 0.003). By multivariable analysis, RS did not have a significant association with OS (hazard ratio (HR) = 0.43, 95% confidence interval (95%CI) = 0.10, 1.83; p = 0.255), nor did positive nodal status (HR = 0.66, 95%CI = 0.09, 5.03; p = 0.692) and unknown nodal status (HR = 1.30, 95%CI = 0.78, 2.17; p = 0.311). There was no difference in OS between the LR and RS groups, with median survival not reached by either group at 10 years (median follow-up = 60.4 months; p = 0.20). CONCLUSIONS: There was no difference in OS between LR and RS for localized PC. RS and nodal status may not impact survival as previously identified, and LR should remain a valid initial surgical approach. Future higher-powered studies are necessary to assess the effects of surgical approaches on morbidity and oncologic outcomes.

Surgery

Madill-Thomsen KS, **Abouljoud M**, Bhati C, Ciszek M, Durlik M, Feng S, Foroncewicz B, **Francis I**, Grąt M, Jurczyk K, Klintmalm G, Krasnodębski M, McCaughan G, Miquel R, Montano-Loza A, **Moonka D**, Mucha K, Myślak M, Pączek L, Perkowska-Ptasińska A, Piecha G, Reichman T, Sanchez-Fueyo A, Tronina O, Wawrzynowicz-Syczewska M, Więcek A, Zieniewicz K, and Halloran PF. The molecular phenotypes of injury, steatohepatitis, and fibrosis in liver transplant biopsies in the INTERLIVER study. *Am J Transplant* 2021; Epub ahead of print. PMID: 34780106. Full Text

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To extend previous molecular analyses of rejection in liver transplant biopsies in the INTERLIVER study (ClinicalTrials.gov #NCT03193151), the present study aimed to define the gene expression selective for parenchymal injury, fibrosis, and steatohepatitis. We analyzed genome-wide microarray measurements from 337 liver transplant biopsies from 13 centers. We examined expression of genes previously annotated as increased in injury and fibrosis using principal component analysis (PCA). PC1 reflected parenchymal injury and related inflammation in the early posttransplant period, slowly regressing over

many months. PC2 separated early injury from late fibrosis. Positive PC3 identified a distinct mildly inflamed state correlating with histologic steatohepatitis. Injury PCs correlated with liver function and histologic abnormalities. A classifier trained on histologic steatohepatitis predicted histologic steatohepatitis with cross-validated AUC=0.83, and was associated with pathways reflecting metabolic abnormalities distinct from fibrosis. PC2 predicted histologic fibrosis (AUC=0.80), as did a molecular fibrosis classifier (AUC=0.74). The fibrosis classifier correlated with matrix remodeling pathways with minimal overlap with those selective for steatohepatitis, although some biopsies had both. Genome-wide assessment of liver transplant biopsies can not only detect molecular changes induced by rejection but also those correlating with parenchymal injury, steatohepatitis, and fibrosis, offering potential insights into disease mechanisms for primary diseases.

Urology

Iqbal U, Jing Z, Ahmed Y, Elsayed AS, **Rogers CG**, Boris RS, Porter JR, Allaf ME, Badani KK, Stifelman MD, Kaouk J, Terakawa T, Hinata N, Aboumohamed A, Kauffman E, Li Q, Abaza R, Guru KAD, Hussein A, and Eun D. Development and Validation of an Objective Scoring Tool for Robot Assisted Partial Nephrectomy: Scoring for Partial Nephrectomy (SPaN). *J Endourol* 2021; Epub ahead of print. PMID: 34809491. Full Text

OBJECTIVE: To develop a structured and objective scoring tool for assessment of robot assisted partial nephrectomy (RAPN): Scoring for Partial Nephrectomy (SPaN). MATERIALS AND METHODS: Content development: RAPN was deconstructed into 6 domains by a multi-institutional panel of 10 expert robotic surgeons. Performance on each domain was represented on a Likert scale of 1-5, with specific descriptions of anchors 1, 3 and 5. Content validation: The Delphi methodology was utilized to achieve consensus about the description of each anchor for each domain in terms of appropriateness of the skill assessed, objectiveness, clarity, and unambiguous wording. The content validity index (CVI) of ≥0.75 was set as cut-off for consensus. Reliability: 15 de-identified videos of RAPN were utilized to determine the inter-rater reliability using linearly weighted percent agreement, and Construct validation of SPaN was described in terms of median scores and odds ratios. RESULTS: The expert panel reached consensus (CVI ≥ 0.75) after 2 rounds. Consensus was achieved for 36 (67%) statements in the first round and 18 (33%) after the second round. The final six-domain SPaN included: Exposure of the kidney; Identification and dissection of the ureter and gonadal vessels; Dissection of the hilum; Tumor localization and exposure; Clamping and tumor resection; and Renorrhaphy. The linearly weighted percent agreement was > 0.75 for all domains. There was no difference between median scores for any domain between attendings and trainees. CONCLUSION: Despite the lack of signification construct validity, SPaN is a structured, reliable and procedure-specific tool that can objectively assesses technical proficiency for RAPN.

Urology

Raison N, Servian P, **Patel A**, Santhirasekaram A, Smith A, Yeung M, Lloyd J, Mannion E, Rockall A, Ahmed H, and Winkler M. Is tumour volume an independent predictor of outcome after radical prostatectomy for high-risk prostate cancer? *Prostate Cancer Prostatic Dis* 2021; Epub ahead of print. PMID: 34845306. Full Text

BACKGROUND: Preoperative PSA, ISUP grade group (GG), prostate examination and multiparametric MRI (mpMRI) form the basis of prostate cancer staging. Unlike other solid organ tumours, tumour volume (TV) is not routinely used aside from crude estimates such as maximum cancer core length. The aim of this study is to assess the role of TV as a marker for oncological outcomes in high-risk non-metastatic prostate cancer. METHODS: A prospectively maintained database of patients undergoing minimally invasive (laparoscopic or robot-assisted laparoscopic) radical prostatectomy at a UK centre between 2007 and 2019 were analysed. A total of 251 patients with NCCN high or very high-risk prostate cancer were identified. Primary outcome measure was time to biochemical recurrence (BCR) and the secondary outcome was time to treatment failure (TTF). TV was measured on the pathological specimen using the stacking method. Multivariable cox regression analysis was used to identify factors predicting BCR and TFF. TV as a predictor of BCR and TFF was further analysed through time-dependent receiver operating

characteristic (ROC) curves. Kaplan-Meier survival estimates were used to evaluate TV cut-off scores. RESULTS: Median follow up was 4.50 years. Four factors were associated with BCR and TFF on multivariable analysis (TV, pathological GG, pathological T stage, positive margin >3 mm). Area under the Curve (AUC) for TV as a predictor of BCR and TTF at 5 years was 0.71 and 0.75, respectively. Including all 4 variables in the model increased AUC to 0.84 and 0.85 for BCR and TFF. A 2.50 cm TV cut off demonstrated a significance difference in time to BCR, $p < 0.001$. CONCLUSIONS: Pathological tumour volume is an independent predictor of oncological outcomes in high risk prostate cancer but does not add significant prognostic value when combined with established variables. However, the option of accurate TV measurement on mpMRI raises the possibility of using TV as useful marker for preoperative risk stratification.

Conference Abstracts

Administration

Stefanou A, **Gardner CW**, and **Rubinfeld IS**. Comparison of Common Minimally Invasive Operations Using Patient Safety Indicators (PSI). *J Am Coll Surg* 2021; 233(5):e98.

Introduction: The PSI 90, is used to monitor hospital safety, quality, and value. It is composed predominantly of PSI 9 (perioperative hemorrhage), 11 (postoperative respiratory failure), 12 (perioperative deep vein thrombosis/pulmonary embolus), and 13 (postoperative sepsis). MIS has been shown to have fewer complications. We aim to evaluate the rates of PSI between MIS in common procedures. Methods: Using a health system database we examined cases that underwent MIS or open appendectomy, cholecystectomy, colectomy, and hysterectomy, and compared them across the four main PSIs over a 2-year period. Operations were compared based on comorbidities, admitting service and procedure. Outcome of interest was surgical approach. Univariate and multivariate analysis was performed in R. Results: Our sample included a total of 1800 MIS and 1580 open operations. Rates of PSI were: PSI 9, 1.8%, PSI 11, 2.7%, PSI 12, 4.2%, and PSI 13, 5.6%. Patients were similar in comorbidities and demographics, with the exception of open procedures being more likely in cancer patients. Univariate analysis found no significant differences across surgical groupings of open vs MIS, or PSI type. Multivariate regression analysis did not show any significant association in MSI operative status and PSI incidence. Conclusion: While minimally invasive surgery has known clinical benefits, this has not translated into a clear improvement across the AHRQ PSI. Additionally, there are still other modifiable factors that would allow for improvement of PSI 90 in minimally invasive surgery.

Cardiology/Cardiovascular Research

Eng M, **Al-Darzi W**, **Villablanca P**, **Frisoli T**, **Gonzalez PE**, **Chiang M**, **Basir M**, **Cowger J**, **Alaswad K**, Prasad A, and **O'Neill W**. TCT-308 Cardiogenic Shock–Associated Cardiorenal Syndrome Improves With the Use of Left Atrial Venous Arterial Extracorporeal Membrane Oxygenation (LAVA-ECMO). *J Am Coll Cardiol* 2021; 78(19):B126.

Background: Cardiorenal syndrome (CRS) can complicate cardiogenic shock (CS) in 60% of cases. A strong predictor of CRS is elevated right atrial (RA) pressure. Left atrial venous arterial extracorporeal membrane oxygenation (LAVA-ECMO) uses a long fenestrated trans-septal cannula that unloads the left and right atrium simultaneously. We describe the impact of rapidly decompressing RA pressure and improved perfusion on renal function with LAVA-ECMO. Methods: From July 2020 to August 2021, 15 patients underwent LAVA-ECMO cannulation at Henry Ford Hospital. Patient characteristics, procedural data, and outcomes were analyzed. Variables are expressed as proportions and medians (interquartile range [IQR]). The Wilcoxon signed rank test was used with 95% confidence intervals for comparisons. Results: The median age was 62 years (IQR: 52-71 years), and 13% were women. Most patients had pure CS (87%) and mixed distributive CS in 2 patients (13%). Most patients had severe valvular heart disease (80%). LAVA-ECMO caused a significant reduction in RA pressure (Figure 1A) and increased pulmonary artery saturation from 48% (IQR: 37-56) to 72% (IQR: 64-81) ($P = 0.002$). Of the 12 patients not receiving renal replacement therapy, 75% patients experienced improvement in renal function, 2 had no change, and 1 worsened. The distribution of serum creatinine (Cr) is shown in Figure 1B between

baseline Cr, day of LAVA-ECMO, 1 day post-LAVA ECMO, and at the time of destination. [Formula presented] Conclusion: LAVA-ECMO lowers RA pressure, improves perfusion, and is associated with rapid reversal of cardiorenal syndrome in most patients. Prospective studies using LAVA-ECMO for cardiogenic shock are warranted. Categories: CORONARY: Hemodynamic Support and Cardiogenic Shock

Cardiology/Cardiovascular Research

Hussain Y, **Gonzalez PE**, Khera R, Banerjee S, Hebbe A, Plomondon M, Waldo S, Pfau S, Curtis J, and Shah S. TCT-100 Real-World Experience and Outcomes of Protected Versus Unprotected Left Main Percutaneous Coronary Intervention: Insights From the VA CART Program. *J Am Coll Cardiol* 2021; 78(19):B42.

Background: Outcomes of protected left main (PLM) and unprotected left main (ULM) percutaneous coronary intervention (PCI) are not well defined in contemporary U.S. practice. Previous studies of real-world data have shown worse in-hospital outcomes of ULM PCI compared with randomized trial data. We used a large national registry to characterize real-world practice and outcomes of left main PCI. Methods: Data were collected from the Veteran Affairs (VA) Clinical Assessment Reporting and Tracking (CART) Program for patients undergoing left main PCI between 2009 and 2019. PLM PCI was defined by the presence of at least 1 functioning bypass graft, and ULM PCI was defined as patients with no bypass grafting. Temporal trends, patient and procedure characteristics, anatomic complexity, and clinical complexity were assessed. A 1-to-1 propensity-matched analysis was performed using common comorbidities and clinical variables. One-year outcome analyses were conducted for major adverse cardiovascular events (MACE), all-cause mortality, rehospitalization for myocardial infarction (MI) and revascularization. Results: Of 4,351 patients undergoing left main PCI, 2,800 were PLM PCI and 1,551 were ULM PCI, of which 1,335 PLM and ULM PCI were included in the propensity matched cohort. Patients undergoing ULM PCI were older, more likely to present with acute coronary syndrome (ACS) and had a higher clinical complexity. In the propensity-matched cohort, there was no difference in age, rate of ACS presentation, burden of comorbidities, or left ventricular ejection fraction. There were no differences in in-hospital adverse events between the 2 groups. At 12 months, MACE occurred more frequently with ULM PCI compared with PLM PCI (25% [334] vs 20% [270]; P = 0.004), and all-cause mortality was also higher (18% [239] vs 14% [185]; P = 0.005). There was no difference in rehospitalization for MI, stroke, or revascularization at 12 months. Conclusion: In the VA Healthcare System, patients undergoing ULM PCI were older and more clinically complex than those undergoing PLM PCI. In the propensity-matched cohort, patients undergoing PLM PCI had better 12 outcomes than those undergoing ULM PCI, but there was a high rate of mortality and MACE at 1 year in both groups, despite a relatively low rate of MI or revascularization. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Kandzari D, **Alaswad K**, Jaffer FA, Brilakis E, Croce K, Kearney K, Spaedy A, Yeh R, Thompson C, Nicholson W, Wyman RM, Riley R, Lansky A, and Karmpaliotis D. TCT-414 Safety and Efficacy of Dedicated Guidewire, Microcatheter, and Guide Catheter Extension Technologies for Chronic Total Coronary Occlusion Revascularization: Primary Results of the Teleflex Chronic Total Occlusion Study. *J Am Coll Cardiol* 2021; 78(19):B169-B170.

Background: Description of procedural outcomes using contemporary techniques that apply specialized coronary guidewires, microcatheters, and guide catheter extensions designed for chronic total occlusion (CTO) percutaneous revascularization is limited. Methods: A prospective, multicenter, single-arm trial was conducted to evaluate procedural and in-hospital outcomes among 150 patients undergoing attempted CTO revascularization using specialized guidewires, microcatheters, and guide extensions. The primary endpoint was defined as successful guidewire recanalization and absence of in-hospital cardiac death, myocardial infarction (MI), or repeat target lesion revascularization (major adverse cardiac events [MACE]). Results: The prevalence of diabetes was 32.7%, of prior MI was 48.0%, and of previous bypass surgery was 32.7%. Average (mean ± SD) CTO length was 46.9 ± 20.5 mm, and mean J-CTO score was 1.9 ± 0.9. Combined radial and femoral arterial access was performed in 50.0% of cases. Devices used included guidewire support microcatheters in 100% and guide catheter extensions in 64.0%, and the

mean number of CTO-specific guidewires per procedure was 5.11 ± 3.52. Overall, procedural success was observed in 75.3% of patients. The rate of successful guidewire recanalization was 94.7%, and the rate of absence of in-hospital MACE was 80.7%. Methods included antegrade (54.0%), retrograde (1.3%), and combined antegrade and retrograde techniques (44.7%). Total mean procedure time was 149 ± 91 minutes, mean radiation dose was 2,219 ± 1,608 mGy, and mean contrast utilization was 205 ± 95 mL. Clinically significant perforation resulting in hemodynamic instability and/or requiring intervention occurred in 16 patients (10.7%). Conclusion: In a multicenter, prospective registration trial, favorable procedural success and early clinical outcomes were achieved in a patient population with high lesion complexity using contemporary techniques and application of dedicated CTO guidewires, microcatheters, and guide catheter extensions. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Karacsonyi J, **Alaswad K**, Karmpaliotis D, Jaffer FA, Choi J, Tsiafoutis I, Kandzari D, Poommipanit P, Khatri J, Elbarouni B, Riley R, Gorgulu S, Kostantinis S, Simsek B, ElGuindy A, Abi-Rafeh N, Goktekin O, Ungi I, Gutierrez A, Avula V, and Brilakis E. TCT-319 Use of Limited Antegrade Subintimal Tracking Technique in Chronic Total Occlusion Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2021; 78(19):B130-B131.

Background: There are limited data on the limited antegrade subintimal tracking (LAST) crossing technique for chronic total occlusion (CTO) percutaneous coronary intervention (PCI). Methods: We analyzed the frequency of use and outcomes of LAST among 2,003 CTO PCIs performed with antegrade dissection and re-entry (ADR) in the PROGRESS-CTO Registry between 2012 and 2021 at 39 centers. Results: LAST was used in 144 cases (7.2%), primary LAST in 113 (5.6%), and secondary LAST in 31 cases (1.5%). The Stingray system was used in 905 cases (45.2%), subintimal tracking and re-entry (STAR) in 333 cases (16.6%), and contrast-guided STAR in 29 cases (1.4%). The mean patient age was 64.2 ± 10 years, 86% were men, and 34.9% had prior coronary artery bypass graft surgery. Cases in which LAST was used were less complex with a lower J-CTO score (2.50 ± 1.32 vs. 2.95 ± 1.10, $P < 0.001$). There was no difference in technical (75.0% vs 78.4%, $P = 0.337$) and procedural success (72.2% vs 75.5%, $P = 0.384$) and major cardiac adverse events (MACEs) (2.08% vs 3.55%, $P = 0.352$) between LAST and non-LAST cases. However, cases in which the LAST technique was used required less procedure and fluoroscopy time (Figure 1A). A primary LAST technique was associated with higher technical and procedural success rates and a similar MACE rate compared with a secondary LAST technique (Figure 1B). Conclusion: LAST is used in 7.2% of ADR CTO PCI cases and is associated with similar technical and procedural success rates and major complication rates but lower procedural and fluoroscopy time compared with ADR cases that did not use LAST. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Kostantinis S, **Alaswad K**, Karmpaliotis D, Jaffer FA, Jaber W, Nicholson W, Rinfret S, Khatri J, Poommipanit P, Karacsonyi J, Vemmou E, Nikolakopoulos I, Avula V, Gutierrez A, Tsiafoutis I, Riley R, Sheikh A, Patel M, Gorgulu S, ElGuindy A, Goktekin O, Abi-Rafeh N, Rangan B, Garcia S, Burke MN, and Brilakis E. TCT-72 Primary Versus Secondary Retrograde Approach in Chronic Total Occlusion Interventions. *J Am Coll Cardiol* 2021; 78(19):B30-B31.

Background: The retrograde approach to coronary chronic total occlusions (CTOs) can be used as the initial crossing strategy (primary retrograde) or after failure of antegrade crossing attempts (secondary retrograde). Methods: We compared baseline clinical and angiographic characteristics and procedural outcomes of primary versus secondary retrograde crossing for CTO percutaneous coronary intervention (PCI) among 2,789 procedures performed at 34 centers between 2012 and 2021. Results: Retrograde CTO PCI was performed as the primary crossing strategy in 1,086 cases (38.9%) and as a secondary approach in 1,703 cases (61.1%). Patients in the primary group had slightly lower left ventricular ejection fraction (49.1% vs 50.4%; $P = 0.018$), were more likely to have had previous coronary artery bypass graft surgery (52.9% vs 38.4%; $P < 0.001$) and had higher J-CTO (3.31 ± 0.98 vs 2.99 ± 1.09; $P < 0.001$) and PROGRESS-CTO (1.47 ± 0.92 vs 1.29 ± 0.99; $P < 0.001$) scores. Technical (81.4% vs 77.3%; $P = 0.01$) and procedural (78.6% vs 74.1%; $P = 0.006$) success rates were higher in the primary retrograde group,

with no difference in in-hospital major adverse events (4.3% vs 4.0%; P = 0.66). Contrast volume (250 [176,347] mL vs 270[190,367] mL; P < 0.001) and procedure time (175 [127,233] min vs 180 [142,236] min; P < 0.001) were lower in the primary group. [Formula presented] Conclusion: Use of retrograde approach as primary crossing strategy is associated with higher rates of technical and procedural success and similar rates of in-hospital major adverse cardiac events compared with secondary retrograde CTO PCI. Categories: CORONARY: Complex and Higher-Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Lansky A, Tirziu D, Pietras C, Moses J, Ohman EM, **O'Neill W**, Grines C, Needham K, Ekono M, Gregory D, and Parise H. TCT-118 Propensity-Adjusted Population-Based Analysis of Impella in Patients Undergoing High-Risk PCI From a Large-Scale Claims Dataset. *J Am Coll Cardiol* 2021; 78(19):B49-B50.

Background: Impella (Abiomed) was FDA approved in 2015 for use in high-risk percutaneous coronary intervention (PCI). We compared post-approval outcomes and costs of Impella versus intra-aortic balloon pump (IABP) support for high-risk PCI in real-world contemporary practice in US hospitals. Methods: From April 2016, to June 2019, 48,179 patients from the Premier Healthcare Database underwent Impella- or IABP-supported PCI at 304 hospitals. We selected patients with nonemergent admission undergoing single PCI procedures with either Impella or IABP support on the day of admission, excluding patients presenting with acute ST-elevation myocardial infarction (STEMI) or cardiogenic shock (CS). Propensity adjustment was used to control baseline differences between treatment groups. Outcomes included in-hospital survival, MI, CS, stroke, bleeding requiring transfusion, acute kidney injury (AKI), index hospitalization length of stay (LOS), and costs. Results: The 2,156 patients meeting nonemergent high-risk PCI criteria were treated with Impella (n = 1,447) or IABP (n = 709). After propensity adjustment, Impella use was associated with improved survival (odds ratio [OR]: 1.55, 95% confidence interval [CI]: 1.02-2.36) and less MI (OR: 0.29; 95% CI: 0.18-0.46) and CS (OR: 0.54; 95% CI: 0.39-0.74). Stroke, bleeding requiring transfusion, and AKI were similar among groups. Impella use was associated with shortened LOS but increased hospitalization costs versus IABP. In-hospital complications, including MI, CS, stroke, and bleeding requiring transfusion, were strong predictors of death. [Formula presented] Conclusion: In this propensity-adjusted analysis, use of Impella during nonemergent high-risk PCI was associated with improved survival and reduced in-hospital MI and CS versus IABP. Categories: CORONARY: Hemodynamic Support and Cardiogenic Shock

Cardiology/Cardiovascular Research

Lemor A, **Dabbagh M**, **Villablanca P**, **Alaswad K**, **O'Neill W**, and **Basir M**. TCT-340 Incidence and Impact of Vascular Complications When Utilizing Mechanical Circulatory Support. *J Am Coll Cardiol* 2021; 78(19):B139.

Background: The use of mechanical circulatory support (MCS) has increased in the past decade with aims to increase survival in patients in shock and to support high-risk procedures. The impact of vascular complications when using MCS is not well studied. Methods: Using the National Inpatient Sample from 2015 to 2018, we identified hospital admissions in which an intra-aortic balloon pump (IABP), Impella (Abiomed), and/or extracorporeal membrane oxygenation (ECMO) were used for any condition. The study outcomes included in-hospital mortality, rates of vascular complications, and any procedures required to treat the complication (ie, angioplasty, open vessel repair, fasciotomy, and/or limb amputation). Results: A total of 204,255 hospitalizations requiring MCS were identified. IABP was the most common MCS used (63.4%) followed by Impella (19.4%) and ECMO (12.0%); 5.2% of hospitalizations used > 1 MCS. The rates of vascular complications with IABP were 3.0%, with Impella they were 6.5%, and with ECMO they were 13.5% (Figure 1). In patients requiring > 1 MCS, there was a 17.1% rate of vascular complication. Predictors of vascular complication include female sex, systolic heart failure, peripheral arterial disease, and use of vasopressors. Total hospital costs were significantly higher in patients with vascular complications compared with those without ($116,094 vs $55,261, P < 0.001). [Formula presented] Conclusion: Vascular complications are associated with higher odds of in-hospital mortality and higher resource utilization in patients treated with MCS. Predictors of vascular complications include larger arteriotomy size, female gender, systolic heart failure, peripheral arterial disease, and use of vasopressors. Categories: CORONARY: Hemodynamic Support and Cardiogenic Shock

Cardiology/Cardiovascular Research

Megaly M, Buda K, **Alaswad K**, Brilakis E, Dupont A, Naidu S, Ohman M, Napp LC, **O'Neill W**, and **Basir M**. TCT-30 A Comparative Analysis of Patient Characteristics in Cardiogenic Shock Trials: Differences Between Randomized Trials and Real-World Registries. *J Am Coll Cardiol* 2021; 78(19):B12.

Background: Cardiogenic shock (CS) is a leading cause of mortality in patients presenting with acute myocardial infarction (AMI). Enrollment of patients into clinical trials, however, is challenging and may not be representative of real-world patients. Methods: We performed a systematic review of studies in patients presenting with AMI-related CS (AMICS) and compared patient characteristics of those enrolled into randomized controlled trials (RCTs) with those in registries. Results: We included 14 RCTs (n = 2,154) and 12 registries (n = 133,617). RCTs included more men (73% vs 67.7%, P < 0.001) compared with registries. Patient enrolled into RCT had fewer comorbidities, including less hypertension (61.6% vs 65.9%, P < 0.001), dyslipidemia (36.4% vs 53.6%, P < 0.001), history of stroke or transient ischemic attack (7.1% vs 10.7%, P < 0.001), and previous coronary artery bypass graft surgery (5.4% vs 7.5%, P < 0.001). Patients enrolled into RCTs also had lower lactate levels (4.7 ± 2.3 vs 5.9 ± 1.9 mmol/L, P < 0.001) and higher mean arterial pressure (73.0 ± 8.8 vs 62.5 ± 12.2 mm Hg, P < 0.001). Percutaneous coronary intervention (PCI) (97.5% vs 58.4%, P < 0.001), multivessel PCI (31% vs 27.4%, P < 0.001), and left ventricular assist devices (LVADs) (11.7% vs 6.9%, P < 0.001) were used more often in RCTs. In-hospital and 30-day mortality were similar in both groups. [Formula presented] Conclusion: RCTs in AMICS tend to enroll fewer women and lower-risk patients when compared with registries. Patients enrolled into RCTs are also more likely to receive aggressive treatment, including PCI and LVAD. Categories: CORONARY: Hemodynamic Support and Cardiogenic Shock

Cardiology/Cardiovascular Research

Megaly M, Khalil M, **Basir M**, McEntegart M, Spratt J, Xu B, **Alaswad K**, and Brilakis E. TCT-417 Outcomes of Successful Versus Failed Contemporary Chronic Total Occlusion Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2021; 78(19):B170-B171.

Background: There are limited contemporary data on the impact of success versus failure on the outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI). Methods: We conducted a systematic review and a meta-analysis of contemporary studies that compared the outcomes in patients who underwent successful versus failed contemporary (2010 onward) CTO PCI. We performed a sensitivity analysis limited to studies that started enrollment after the publication of the hybrid algorithm in 2012. Results: We included 5 studies with a total of 6,084 patients (successful CTO PCI, n = 4,861; failed CTO PCI, n = 1,223). During a median follow-up period of 12 months (range: 6-60 months), successful CTO PCI was associated with a lower risk for major adverse cardiovascular events (MACE) (odds ratio [OR]: 0.61; 95% confidence interval [CI]: 0.41-0.92; P = 0.02; I2 = 63%) and all-cause death (OR: 0.57; 95% CI 0.33-0.99; P = 0.05; I2 = 60%). Both groups had similar risk for myocardial infarction (OR: 0.69; 95% CI 0.43-1.10; P = 0.38; I2 = 80%), target vessel revascularization (OR: 0.56; 95% CI 0.25-1.27; P = 0.17; I2 = 80%), and stroke (OR: 0.52; 95% CI 0.14-1.91; P = 0.33; I2 = 0%). [Formula presented] Conclusion: In contemporary practice, successful CTO PCI was associated with a lower incidence of MACE driven by lower all-cause mortality compared with failed CTO PCI at a median follow-up of 1 year. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Megaly M, Sedhom R, Elbadawi A, Saad M, Cavalcante J, Sengupta J, and Garcia S. TCT-195 In-Hospital and Readmission Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol* 2021; 78(19):B80.

Background: Permanent pacemaker implantation (PPMI) is a known complication of TAVR. It is unclear if recent efforts and procedure advancements have resulted in lower in-hospital PPMI rates or a shift toward outpatient PPMI after the index hospitalization. Methods: We used the Nationwide Readmissions Database to analyze post-TAVR PPMI rates from 2016 to 2018. All trend analyses were performed using the Poisson regression method. We performed multivariate logistic regression analysis to identify

predictors of 30-day readmission for PPMI. Results: A total of 7,848 records (national estimate of 14,038 records) out of 70,245 TAVR records (national estimate of 126,794 records) (11.1%) underwent PPMI during the index hospitalization. There was a significant trend toward lower PPMI over the study period (12.3% in the first quarter of 2016 to 10.6% in the last quarter of 2018) (P trend < 0.001). 862 patients were readmitted for PPMI (national estimate of 1,602 records, 1.5%). There was no significant change in the trend of patients readmitted for PPMI from 2016 to 2018. Bicuspid aortic valve, history of atrial fibrillation or flutter, morbid obesity, and severe renal disease were independently associated with 30-day readmission for PPMI, while female sex and having the procedure at a teaching hospital were protective against readmission for PPMI. [Formula presented] Conclusion: Over the study period from 2016 to 2018, the overall PPMI rate during the index hospitalization was 11.1% with a decreasing trend, and readmission for PPMI was 1.5% with a stable trend. Important predictors of readmission for PPMI included bicuspid aortic valve, history of atrial fibrillation or flutter, morbid obesity, and severe renal disease. Categories: STRUCTURAL: Valvular Disease: Aortic

Cardiology/Cardiovascular Research

Megaly M, Sedhom R, Elbadawi A, Saad M, Omer M, Brilakis E, **Basir M**, Jaffer FA, **Zaidan M**, **Alqarqaz M**, and **Alaswad K**. TCT-288 Trends and Outcomes of Utilization of Thrombectomy During Primary Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2021; 78(19):B118-B119.

Background: The aim of this study was to describe the national trends and outcomes of contemporary thrombectomy use for primary percutaneous coronary intervention (PCI) from 2016 to 2018. Methods: We queried the Nationwide Readmission Database from January 2016 to December 2018 to identify patients who underwent primary PCI and thrombectomy. We conducted a multivariate regression analysis to identify variables associated with in-hospital mortality and stroke in patients undergoing primary PCI and those who underwent thrombectomy. Results: We identified 409,910 total hospitalizations who underwent primary PCI (Figure 1). Thrombectomy was used in 62,446 records (15.2%) with no change in the trend over the study period (P trend = 0.52). Thrombectomy was used more in patients who had more cardiogenic shock and use of mechanical circulatory devices. The overall incidences of in-hospital mortality and stroke were 5.6% and 1.1%, respectively. The incidences of in-hospital mortality (6.7% vs 5.4%, P < 0.001) and strokes (1.3% vs 1.0%, P < 0.001) were higher in the thrombectomy group. On multivariable regression analysis adjusting for high-risk features, thrombectomy was not independently associated with in-hospital mortality (odds ratio [OR]: 1.04; 95% confidence interval [CI]: 0.99-1.08, P = 0.100) but was associated with a higher risk of stroke (OR: 1.186; 95% CI: 1.097-1.283, P < 0.001). [Formula presented] Conclusion: During primary PCI, thrombectomy was used in 1 of 6 cases, and its use has been stable over 2016 to 2018. The use of thrombectomy was associated with a higher risk of stroke but not in-hospital death. Categories: CORONARY: Coronary Atherectomy, Plaque Modification, and Thrombectomy

Cardiology/Cardiovascular Research

Megaly M, Tannenbaum E, Okeson B, Dworak M, Garberich R, Sharkey S, Tannenbaum M, Smith T, Henry T, and Garcia S. TCT-470 Incidence and Clinical Characteristics of Stroke in Patients Presenting With STEMI: Insights From the Midwest STEMI Consortium. *J Am Coll Cardiol* 2021; 78(19):B193.

Background: Contemporary real-world data on stroke in patients presenting with ST-segment elevation myocardial infarction (STEMI) are scarce. Methods: We evaluated the incidence and etiology of stroke from 2003 to 2019 in 4 large regional STEMI programs in the upper Midwest that use similar transfer and treatment protocols. We described the clinical characteristics and discharge data of stroke patients. Results: In total, 12,868 patients presented with STEMI during the study period. Stroke occurred in 98 patients (0.76%). The stroke etiology was ischemic in 74.5%, hemorrhagic in 21.4%, and mixed in 3%. Most of the postprocedural strokes were identified >24 hours after primary percutaneous coronary intervention (PCI) (43%). The median time to stroke symptoms after PCI was 14 hours (interquartile range: 4-72 hours). Stroke occurred before primary PCI in 13% of patients and during the procedure in 5%. On the basis of the review of medical records and neurology adjudication, the stroke etiology was determined to be procedure related, related to anoxic brain injury, or atrial fibrillation in 21%, 10%, and 7.1% of cases, respectively. A stroke after STEMI is associated with significantly higher in-hospital mortality (18%). Approximately 49.2% of patients who had in-hospital strokes were discharged to nursing

facilities or assisted living facilities. Conclusion: In patients presenting with STEMI, the risk for stroke is low (0.76%). One in 5 strokes associated with STEMI was hemorrhagic, and approximately 1 in 10 patients had their strokes before PCI. A stroke after STEMI is associated with significantly higher in-hospital mortality (18%) and half of the survivors were discharged to a facility. Categories: CORONARY: Acute Myocardial Infarction

Cardiology/Cardiovascular Research
Megaly M, Zordok M, Mentias A, Chugh Y, **Basir M**, Burke MN, Karmpaliotis D, Azzalini L, **Alaswad K**, and Brilakis E. TCT-504 Complications and Failure Modes of Covered Coronary Stents: Insights From the MAUDE Database. *J Am Coll Cardiol* 2021; 78(19):B205-B206.

Background: Data on the mechanisms of failure of covered coronary stents (Graftmaster and PK Papyrus) are limited. Methods: We queried the Manufacturer and User Facility Device Experience (MAUDE) database between August 2018 (when the PK Papyrus stent was US Food and Drug Administration approved) and December 2020 for reports on covered coronary stents. Results: We identified 299 reports in the MAUDE database (after excluding duplicates, peripheral vascular reports, and incomplete records) (Graftmaster, n = 225; PK Papyrus, n = 74). The most common mechanism of failure of covered stents was failure to deliver the stent (46.2%), followed by stent dislodgement (22.4%) and failure to seal the perforation (19.7%). Failure to deliver the stent was more often reported with the Graftmaster compared with the PK Papyrus (59.1% vs 6.8%; P < 0.001). Stent dislodgement was more often reported with the PK Papyrus compared with the Graftmaster (75.7% vs 4.9%; P < 0.001) and was managed by device retrieval or by crushing the stent. [Formula presented] Conclusion: The most common failure mechanisms of covered stents are failure of delivery, stent dislodgement, and failure to seal the perforation. Failure of delivery was more common with the Graftmaster, while stent dislodgement was more common with the PK Papyrus. Further improvements in covered stent design are needed to optimize deliverability and minimize the risk for complications. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Nikolakopoulos I, Quadros A, Dens J, Rafeh NA, Agostoni P, **Alaswad K**, Avran A, Belli K, Campos C, Carlino M, Choi J, De Los Santos FD, ElGuindy A, Jaffer FA, Karmpaliotis D, Khatri J, Khelimskii D, Knaapen P, Krestyaninov O, La Manna A, Lamelas P, Ojeda S, Padilla L, Piccaro de Oliveira P, Rinfret S, Santiago R, Spratt J, Walsh S, Kostantinis S, Simsek B, Karacsonyi J, Rangan B, Vemmou E, Brilakis E, and Azzalini L. TCT-71 Characteristics and Outcomes of Men and Women Undergoing Chronic Total Occlusion Percutaneous Coronary Intervention: Individual Patient Data Pooled Analysis of 4 Multicenter Registries. *J Am Coll Cardiol* 2021; 78(19):B29-B30.

Background: Sex-specific outcomes of chronic total occlusion percutaneous coronary intervention (CTO PCI) have received limited study. Methods: We examined the clinical and angiographic characteristics and procedural outcomes of 11,525 CTO PCIs performed on 11,421 patients (1,901 women and 9,520 men) at 107 centers in Europe, North America, Latin America, and Asia between 2012 and 2020, pooling patient-level data from 4 multicenter registries. Results: Women comprise 20% of CTO PCI patients, and their share among all CTO PCI patients has increased over time (Figure 1). Women are older, more likely to have diabetes, and to present with lower angiographic complexity scores (Table 1). Women have higher technical (88% vs 85%, P < 0.001) and procedural success (86% vs 84%, P = 0.03) and higher rates of tamponade (1.1% vs 0.7%, P = 0.04). Procedural success in women was more frequently achieved by antegrade wiring. [Formula presented] [Formula presented] Conclusion: Women who undergo CTO PCI have less complex lesions than men. CTO PCI in women is associated with higher success rates but also higher rates of tamponade. Categories: CORONARY: Complex and Higher-Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Sedhom R, Abdelmaseeh P, Haroun M, **Megaly M**, **Basir M**, and Jaber W. TCT-454 Complications and Failure Modes of Inari FlowTriever Aspiration System in Pulmonary Embolism: Insights From the MAUDE Database. *J Am Coll Cardiol* 2021; 78(19):B187.

Background: The Inari FlowTriever aspiration system (Inari Medical) gained US Food and Drug Administration approval in May 2018 for use in pulmonary embolism. Data on its failure mechanisms are limited. Methods: We investigated the Manufacturer and User Facility Device Experience database for reports on Inari FlowTriever aspiration system failure from June 2018 to May 2021. The outcomes of this study were the device failure modes and their clinical consequences. Results: A total of 27 reports were found during the study period. After excluding duplicate reports (n = 6), incomplete ones (n = 1), and those of deep venous thrombosis without pulmonary embolism (n = 4), our final cohort included 16 reports. Injury to the pulmonary vessels occurred in 6 reports (37.5%), with pulmonary perforation being the most common type of injury, occurring in 3 reports (18.8%), followed by pulmonary pseudoaneurysm in 2 reports (12.5%) and pulmonary dissection in 1 report (6.3%). Hemoptysis occurred in 4 reports (25%) and pericardial effusion in 3 reports (18.8%), and blood transfusion was needed in 5 reports (31.3%). Cardiopulmonary arrest occurred in 11 (68.8%) and death in 10 (62.5%) reports. Conclusion: We found that reports of Inari FlowTriever Aspiration System failure were rare (16 over 3 years). However, failure reports were serious and included pulmonary artery injury and hemoptysis. Careful catheter manipulation may help avoid such complications. Categories: ENDOVASCULAR: Pulmonary Embolism and Pulmonary Hypertension

Cardiology/Cardiovascular Research

Sedhom R, **Megaly M**, Saad M, Elbadawi A, Witzke CF, Garcia S, and Latib A. TCT-174 Transcatheter Edge-to-Edge Repair of the Tricuspid Valve: The US Experience. *J Am Coll Cardiol* 2021; 78(19):B72.

Background: Surgery for isolated tricuspid regurgitation is associated with high morbidity and mortality and is rarely performed. Transcatheter edge-to-edge repair (TEER) of the tricuspid valve (TV) is an attractive alternative to TV surgery. We aimed to examine the trends in utilization and outcomes of TV TEER. Methods: The Nationwide Readmissions Database was queried using the International Classification of Diseases, Tenth Revision, procedure code for TEER of TV for the years 2016-2018. The main outcomes were trends in utilization and in-hospital all-cause mortality. Results: We identified 420 hospitalizations for TEER of the TV. There was an uptrend in its utilization over time: from 13 cases in the first quarter of 2016 to 98 cases in the last quarter of 2018 (P trend < 0.001). Concomitant TEER of the MV was performed in 38.1% of admissions. The overall in-hospital mortality was 1.7%, and cardiogenic shock occurred in 7.3%, complete atrioventricular block in 2.5%, and tamponade in 1.2% of admissions. Surgical TV replacement was needed in 1.5% of admissions, none of which patients died during the index hospitalization. Unplanned rehospitalizations were common at 30 days (17.4%), 41% of them due to heart failure. There was no difference in in-hospital mortality between isolated TV TEER and combined mitral valve and TV TEER (2.3% vs 0.6%; P = 0.260). Conclusion: In this nationwide study, there was an increase in the utilization of TV TEER. TV TEER was associated with low rates of in-hospital mortality and morbidity; however, the rate of urgent readmission remains high, mainly owing to heart failure. The ongoing TRILUMINATE Pivotal Trial and future trials will give a better understanding of the role of TV clipping for the management of severe TR. Categories: STRUCTURAL: Valvular Disease: Tricuspid

Cardiology/Cardiovascular Research

Vemmou E, Quadros A, Dens J, Rafeh NA, Agostoni P, **Alaswad K**, Avran A, Belli K, Campos C, Carlino M, Choi J, De Los Santos FD, ElGuindy A, Jaffer FA, Karmpaliotis D, Khatri J, Khelimskii D, Knaapen P, Krestyaninov O, La Manna A, Lamelas P, Ojeda S, Padilla L, Pan M, Piccaro de Oliveira P, Rinfret S, Santiago R, Spratt J, Walsh S, Kostantinis S, Simsek B, Karacsonyi J, Nikolakopoulos I, Rangan B, Brilakis E, and Azzalini L. TCT-68 Chronic Total Occlusion Percutaneous Coronary Intervention for Patients With Previous CABG: Insights From a Pooled Analysis of 4 Multicenter Registries. *J Am Coll Cardiol* 2021; 78(19):B28.

Background: The outcomes of percutaneous coronary intervention (PCI) for chronic total occlusions (CTOs) in patients with previous coronary artery bypass graft surgery (CABG) have received limited study. Methods: We examined the clinical angiographic characteristics and procedural outcomes of 11,503 CTO-PCIs performed on 11,397 patients at 108 US and international centers between 2012 and 2020, pooling patient-level data from 4 multicenter registries. In-hospital major adverse cardiovascular events included death, myocardial infarction, stroke, and tamponade. Results: There were 2,776 patients with previous CABG (24.4% of the total cohort). Patients with previous CABG were older (68 vs 64 years

old, P < 0.01) and more likely to have diabetes (48% vs 36%, P < 0.001). Patients with previous CABGs had higher J-CTO scores (2.7 ± 1.2 vs 2.1 ± 1.3, P < 0.001) and more proximal-cap ambiguity (43% vs 32%, P < 0.001) compared with patients who did not have previous CABGs. Antegrade wiring was the most used strategy in the previous CABG group (46% vs 66%), followed by retrograde crossing (35% vs 18%) and antegrade dissection and re-entry (19% vs 15%, P < 0.001). Patients with previous CABG required more contrast material (250 [175,350] vs 240 [170,331] mL, P < 0.001), and intravascular imaging was used more often (36% vs 33%, P = 0.02). Technical (80% vs 87%, P < 0.001) and procedural (79% vs 86%, P < 0.001) success rates were lower in patients who had previous CABGs but had similar incidence of in-hospital major adverse cardiovascular events (MACE) (2.5% vs 2.4%, P = 0.77). [Formula presented] Conclusion: CTO-PCI in patients with previous CABG is associated with lower technical and procedural success but similar in-hospital rates of major adverse cardiovascular events. Categories: CORONARY: Complex and Higher-Risk Procedures for Indicated Patients (CHIP)

Dermatology

Gooderham M, Deleuran M, **Gold LS**, Calimlim B, Zeng J, Takemoto S, Raymundo E, and Weidinger S. Improvement in patient global impression measures with upadacitinib with or without topical corticosteroids in moderate to severe atopic dermatitis: Results from placebo-controlled phase 3 studies. *Exp Dermatol* 2021; 30:16-17.

Diagnostic Radiology

Dai Z, Jambor I, Taimen P, **Pantelic M**, **Elshaikh MA**, **Dabaja A**, **Rogers C**, Ettala O, Boström P, Aronen H, Merisaari H, and **Wen N**. Accurate Prostate Cancer Detection and Segmentation Using Non-Local Mask R-CNN With Histopathological Ground Truth. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S45.

Z. Dai, Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, United States

Purpose/Objective(s): We aim to develop deep learning (DL) models to accurately detect and segment intraprostatic lesions (IL) on biparametric MRI (bp-MRI). Materials/Methods: Three patient cohorts with ground truth IL delineated on different modalities were collected. 158 patients from two datasets had suspicious ILs delineated based on bp-MRI: 97 patients were from PROSTATEx-2 Challenge with biopsy result independent from bp-MRI based delineation, 61 patients were from IMPROD clinical Trial with biopsy done for each delineation; 64 patients from IMPROD clinical Trial had ILs identified and delineated by using whole mount prostatectomy specimen sections as reference standard; 40 private patients were unlabeled. We proposed a non-local Mask R-CNN to improve segmentation accuracy by addressing the imperfect registration issue between MRI modalities. We also proposed to post aggregate 2D predictions to estimate IL volumes within the whole prostatic gland and keep top-5 3D predictions for each patient. In order to explore the small dataset problem, we employed different learning techniques including transfer learning and semi-supervised learning with pseudo labelling. We experimented with two label selection strategies to see how they affected model performance. The first strategy kept only one prediction by referring to biopsy result, in order to minimize false positives; while the second strategy kept all top-5 predictions. 3D top-5 detection rate, dice similarity coefficient (DSC), 95 percentile Hausdorff Distance (95 HD, mm) and true positive ratio (TPR) were our evaluation metrics. We compared DL model prediction with prostatectomy-based ground truth delineation to accurately evaluate the boundary and malignancy level. We separately evaluated ILs of all Gleason Grade Group (GGG) and clinically significant ILs (GGG > 2). Results: Main results are summarized in Table 1. Conclusion: Our proposed method demonstrates state-of-art performance in the detection and segmentation of ILs and shows great effectiveness for clinically significant ILs.

Emergency Medicine

Vohra V, and **Baltarowich L**. A descriptive case series of a single poison center's experience of Gyromitra spp. ingestions over a 19-year period. *Clin Toxicol* 2021; 59(11):1126-1126.

Gastroenterology

Chuong MD, **Kirsch C**, Herrera R, Rubens M, Gungor G, **Schaff EM**, **Dolan J**, **Kim J**, Mittauer KE, Kotecha R, Gutierrez A, **Doemer AJ**, Ugurluer G, **Kwon D**, **Khan G**, Alvarez D, Ucar A, Asbun H, Ozyar E, and **Parikh PJ**. Long-Term Multi-Institutional Outcomes of 5-Fraction Ablative Stereotactic MR-Guided

Adaptive Radiation Therapy (SMART) for Inoperable Pancreas Cancer With Median Prescribed Biologically Effective Dose of 100 Gy10. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S147-S148.

M.D. Chuong, Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, FL, United States

Purpose/Objective(s): Randomized trials have shown improved local control (LC) but no overall survival (OS) benefit with the addition of non-ablative radiation therapy (RT) dose compared to chemotherapy (CT) alone for pancreas cancer (PCa). Emerging data suggest that dose-escalated RT may improve LC and OS. A few studies suggest that stereotactic magnetic resonance-guided adaptive RT (SMART) can facilitate the safe delivery of ablative dose for inoperable PCa, although long-term outcomes are not well understood. Materials/Methods: Inoperable PCa patients who received SMART were identified from the RSSearch Registry. Patients with < 3 months (mo.) follow-up after SMART were excluded. LC, progression free survival (PFS), and OS were estimated using the Kaplan-Meier method. LC was evaluated according to RECIST 1.1 criteria. Acute toxicity was considered within 90 days of SMART and evaluated by CTCAE v4 criteria. Results: A total of 148 PCa patients were treated on a 0.35T MR LINAC across 3 institutions between 2018-2020. Median age was 68 years (range 47-91), and 73.6% had ECOG 0-1 performance status. Patients had locally advanced (57.4%), borderline resectable (29.1%), or medically inoperable (13.5%) disease. Median CA19-9 at diagnosis was 202.1 U/mL (range 0.9-21,281). Induction CT was delivered to 89.2% for a median 3.9 mo (range 0.2-11.3); FOLFIRINOX (52.7%) or gemcitabine/nab-paclitaxel (23.4%) were common. Median prescribed RT dose was 50 Gy (range 40-50) in 5 fractions, mostly in consecutive days (96.6%) and in breath hold (95.3%). Median biologically effective dose (BED10) was 100 Gy10. All patients were treated with real-time tissue tracking and automated beam gating without fiducial markers. An elective target volume was rarely used (25%). Pancreaticoduodenectomy was performed in 23% at a median 46 days (range 34-304) after SMART. Median follow-up was 16 mo. from diagnosis for all patients (range, 4-39). Median, 1-year, and 2-year LC was not reached (NR), 94.6%, and 83%, respectively. Median, 1-year, and 2-year PFS was 18 mo., 72%, and 35.9%, respectively. Median, 1-year, and 2-year OS was 26 mo., 82%, and 52.7%, respectively. Acute and late grade 3 toxicity possibly related to SMART occurred in 4.1% and 12.8%, respectively. There was no reported grade 4+ toxicity. Conclusion: To our knowledge, this is the largest reported analysis of 5-fraction SMART for inoperable PCa. These data add to the evidence that ablative radiation dose may improve long-term outcomes including OS. Prospective evaluation of this novel approach is warranted with attention directed at optimizing patient selection, understanding the clinical significance of cumulative dose delivered across all adapted fractions, and assessing treatment response after the delivery of ablative dose.

Gastroenterology

Liang E, **Kirsch C**, **Gardey V**, **Burmeister C**, **Dragovic J**, and **Parikh PJ**. 90-Day Hospitalization as a Surrogate for Overall Survival in Hepatocellular Carcinoma (HCC) Patients Treated With Magnetic Resonance-Guided Liver Stereotactic Body Radiation Therapy: Results of a Single-Center Retrospective Study. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e53-e54.

E. Liang, Henry Ford Health System, Detroit, MI, United States

Purpose/Objective(s): With the increased utilization of stereotactic body radiation therapy (SBRT) for the management of hepatocellular carcinoma (HCC), it is important to have accurate prognostic factors for survival to guide treatment management decisions. Here, we examine 90-day hospitalization as a prognostic factor in addition to established staging systems including the albumin-bilirubin (ALBI) grade, Child-Pugh score, and Barcelona Clinic Liver Cancer (BCLC) stage. Materials/Methods: This retrospective single-institution study analyzed 95 patients with HCC treated with SBRT from August 2017 to September 2020. Overall survival (OS) rates were retrospectively analyzed from treatment completion date to death date or last follow-up. Patients were censored from further analysis if subsequent SBRT courses were administered. Patient characteristics, 90-day hospitalization, ALBI grade, Child-Pugh score, and BCLC liver stage were analyzed with the Cox proportional hazard model and log-rank test; any significant factors on univariate analysis were subsequently analyzed in the multivariate analysis. Results: Median overall survival among the entire cohort was 67 months (range 0-38 months). Univariate

predictors of overall survival included patient sex (P = 0.02), performance status (P = 0.03), Child-Pugh score (P = 0.003), ALBI grade (P < 0.0001), as well as 90-day hospitalization (P < 0.0001). However, 90-day hospitalization itself was associated with patient male gender (26.9% vs 7.1%; P = 0.03), performance status (P < 0.0001), Child-Pugh score (P = 0.003), ALBI grade (P = 0.003), and BCLC stage (P = 0.002). In the multivariate analysis, patient male sex (P = 0.02), ALBI grade 3 (P = 0.05), and 90-day hospitalization (P = 0.03) remained significant. Conclusion: 90-day hospitalization is a significant predictor of overall survival among patients treated with SBRT for HCC. 90-day hospitalization could be used as an early endpoint in trials evaluating liver SBRT.

Gastroenterology

Schaff EM, **Kirsch C**, **Gartrelle KJ**, **Li P**, **Khan G**, **Shah R**, **Movsas B**, **Parikh PJ**, **Siddiqui F**, and **Kwon D**. Magnetic Resonance Guided Stereotactic Ablative Radiation Therapy vs. Chemoradiation for Borderline and Locally Advanced Pancreatic Cancer: Single Institution Overall Survival Comparison. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e74-e75.

E.M. Schaff, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Several academic institutions have investigated stereotactic MR guided adaptive radiation therapy (SMART) to safely dose escalate for locally advanced and borderline resectable pancreatic cancer with initial favorable toxicity and survival outcomes. In 2018 our institution began to evaluate SMART on trial in borderline and locally advanced patients. We previously presented toxicity outcomes for standard fractionated chemoradiation (chemoRT) and SMART groups with acute grade 3+ GI toxicity in 28% vs 11% (P = 0.18) and late toxicity 43% vs 36% (P = 0.77). The purpose of this abstract was to compare overall survival (OS) between chemoRT and SMART. Materials/Methods: In this IRB approved analysis, we retrospectively reviewed 115 consecutive patients from 2017-2020 with locally advanced or borderline resectable pancreatic cancer who were treated with neoadjuvant radiation therapy. Initially all patients received chemoRT to a dose of 50.4 Gy in 28 fractions. In September 2018 we began to investigate SMART (50Gy in 5 fractions) for these patients. OS was evaluated by Kaplan-Meier and log-rank test. Univariate and multivariate analysis was also performed on multiple treatment variables. Results: Of the patients included, 30 received chemoRT and 85 received SMART. Median follow up for the chemoRT group was 32.8 months and for SMART was 14.9 months from last day of RT. Groups did not have significant differences in age, gender, tumor location, or initial CA 19-9. Pancreatectomy was performed in 13.3% vs 18.8% of patients in chemoRT and SMART groups. Per NCCN.1.2021 staging in the chemoRT group 33.3% were borderline (BL), 50% were locally advanced (LA), and 16.7% medically unresectable (MU) as compared to 24.7% BL, 49.4% LA, and 25.9% MU in the SMART group. Mean months of neoadjuvant chemo was slightly higher in the SMART group at 3.6 vs 2.3 months. Patients in the chemoRT arm were 36.7% African American vs 15.3% in the SMART group. When evaluated using Kaplan-Meier and log-rank test there was no difference in OS between groups (P = 0.95). Median OS from last day of RT in chemoRT and SMART groups was 10.7 vs 12.1 months. On univariate and multivariate analyses pancreatectomy was associated with improved OS, and both N2 disease at diagnosis and poor performance status (ECOG 2+) were associated with worse OS. Conclusion: Dose escalated SMART for locally advanced, borderline, and medically inoperable pancreatic cancer shows similar OS to standard fractionated chemoRT at a median 14.9 month follow up in our single institution analysis. With similar toxicity and OS between treatment modalities, SMART may be preferred due to the single week treatment course in a disease with overall very poor prognosis.

Hematology-Oncology

Chuong MD, **Kirsch C**, Herrera R, Rubens M, Gungor G, **Schaff EM**, **Dolan J**, **Kim J**, Mittauer KE, Kotecha R, Gutierrez A, **Doemer AJ**, Ugurluer G, **Kwon D**, **Khan G**, Alvarez D, Ucar A, Asbun H, Ozyar E, and **Parikh PJ**. Long-Term Multi-Institutional Outcomes of 5-Fraction Ablative Stereotactic MR-Guided Adaptive Radiation Therapy (SMART) for Inoperable Pancreas Cancer With Median Prescribed Biologically Effective Dose of 100 Gy10. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S147-S148.

M.D. Chuong, Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, FL, United States

Purpose/Objective(s): Randomized trials have shown improved local control (LC) but no overall survival (OS) benefit with the addition of non-ablative radiation therapy (RT) dose compared to chemotherapy (CT) alone for pancreas cancer (PCa). Emerging data suggest that dose-escalated RT may improve LC and OS. A few studies suggest that stereotactic magnetic resonance-guided adaptive RT (SMART) can facilitate the safe delivery of ablative dose for inoperable PCa, although long-term outcomes are not well understood. Materials/Methods: Inoperable PCa patients who received SMART were identified from the RSSearch Registry. Patients with < 3 months (mo.) follow-up after SMART were excluded. LC, progression free survival (PFS), and OS were estimated using the Kaplan-Meier method. LC was evaluated according to RECIST 1.1 criteria. Acute toxicity was considered within 90 days of SMART and evaluated by CTCAE v4 criteria. Results: A total of 148 PCa patients were treated on a 0.35T MR LINAC across 3 institutions between 2018-2020. Median age was 68 years (range 47-91), and 73.6% had ECOG 0-1 performance status. Patients had locally advanced (57.4%), borderline resectable (29.1%), or medically inoperable (13.5%) disease. Median CA19-9 at diagnosis was 202.1 U/mL (range 0.9-21,281). Induction CT was delivered to 89.2% for a median 3.9 mo (range 0.2-11.3); FOLFIRINOX (52.7%) or gemcitabine/nab-paclitaxel (23.4%) were common. Median prescribed RT dose was 50 Gy (range 40-50) in 5 fractions, mostly in consecutive days (96.6%) and in breath hold (95.3%). Median biologically effective dose (BED10) was 100 Gy10. All patients were treated with real-time tissue tracking and automated beam gating without fiducial markers. An elective target volume was rarely used (25%). Pancreaticoduodenectomy was performed in 23% at a median 46 days (range 34-304) after SMART. Median follow-up was 16 mo. from diagnosis for all patients (range, 4-39). Median, 1-year, and 2-year LC was not reached (NR), 94.6%, and 83%, respectively. Median, 1-year, and 2-year PFS was 18 mo., 72%, and 35.9%, respectively. Median, 1-year, and 2-year OS was 26 mo., 82%, and 52.7%, respectively. Acute and late grade 3 toxicity possibly related to SMART occurred in 4.1% and 12.8%, respectively. There was no reported grade 4+ toxicity. Conclusion: To our knowledge, this is the largest reported analysis of 5-fraction SMART for inoperable PCa. These data add to the evidence that ablative radiation dose may improve long-term outcomes including OS. Prospective evaluation of this novel approach is warranted with attention directed at optimizing patient selection, understanding the clinical significance of cumulative dose delivered across all adapted fractions, and assessing treatment response after the delivery of ablative dose.

Hematology-Oncology

Cook AE, **Modh A**, **Ali H**, **Sheqwara J**, **Chang S**, **Ghanem T**, **Momin S**, **Wu V**, **Tam S**, **Han X**, **Fakhoury L**, **Movsas B**, and **Siddiqui F**. Randomized Phase III, Double-Blind, Placebo-Controlled Study of Prophylactic Gabapentin for the Reduction of Radiation Therapy-Induced Pain During the Treatment of Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S61-S62.

A.E. Cook, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): We sought to determine if prophylactic gabapentin usage in patients undergoing definitive concurrent chemoradiotherapy (chemoRT) for oropharyngeal cancer improves patient-reported quality of life (QOL) metrics, opioid analgesic requirements, and feeding tube (FT) placement. Materials/Methods: This double-blind, randomized phase III study for patients with AJCC 7th ed stage III-IV oropharyngeal squamous cell carcinoma undergoing concurrent chemoRT randomly allocated patients to prophylactic gabapentin (600 mg TID) or placebo, stratified by smoking status. All patients received 70 Gy in 35 fx using IMRT. The primary endpoint was change in Patient-Reported Oral Mucositis Symptom (PROMS) scores from baseline over the study period. Opioid requirements (average over the entire study period and change from baseline, converted to daily morphine equivalents [DME]), FT placement, and other patient-reported QOL metrics (FACT-HN and PRO-CTCAE) were assessed. Questionnaires were administered at baseline, weekly during RT treatments, and at 6-week post-RT follow-up (f/u). Patients were considered compliant if they took at least 12 doses in any given week (self-reported). Repeated measures ANOVA was used to detect differences in PROMS scores and change in opioid use from baseline. Wilcoxon-rank sum tests were used to compare average opioid use, FACT-HN, and PRO-CTCAE scores. Chi-square test was used to compare FT placement. A P value less than 0.05 was considered statistically significant. Results: There were 65 patients enrolled in the study and 7 withdrew consent, leaving 58 patients to be analyzed. Baseline characteristics were well-balanced, and only 1 patient was considered non-compliant. All patients completed RT as planned. No significant difference

was found in PROMS scores between the two groups (P = 0.130). FT placement was significantly higher in the gabapentin vs placebo arm (64.3% vs 33.3%, P = 0.003). Of the FTs placed, 96% were Dobhoff tubes. There was no significant difference in terms of average opioid use (median 22.8 DME [IQR 12.8-36.5] vs 15.8 DME [IQR 8.3-32.4], P = 0.412) or change in opioid use (P = 0.818) for gabapentin vs placebo, respectively. For the FACT-HN questionnaire, the only significant difference noted was in the functional well-being index with the gabapentin arm having a significant decrease in scores from baseline to f/u (median -6 [IQR -10 to -1.5] vs -1 [IQR -5.75 to 5], P = 0.017) with lower scores suggesting poorer QOL. PRO-CTCAE scores increased significantly at f/u from baseline for gabapentin vs placebo (median 6 [IQR 3 to 11] vs 1 [IQR -2 to 6.5], P = 0.014) with higher scores suggesting worse QOL. Conclusion: This study suggests that prophylactic gabapentin is not effective in improving pain related to mucositis during chemoRT in patients with oropharyngeal squamous cell carcinoma, and other strategies should be evaluated to minimize opioid usage in this patient population.

Hematology-Oncology

Schaff EM, **Kirsch C**, **Gartrelle KJ**, **Li P**, **Khan G**, **Shah R**, **Movsas B**, **Parikh PJ**, **Siddiqui F**, and **Kwon D**. Magnetic Resonance Guided Stereotactic Ablative Radiation Therapy vs. Chemoradiation for Borderline and Locally Advanced Pancreatic Cancer: Single Institution Overall Survival Comparison. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e74-e75.

E.M. Schaff, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Several academic institutions have investigated stereotactic MR guided adaptive radiation therapy (SMART) to safely dose escalate for locally advanced and borderline resectable pancreatic cancer with initial favorable toxicity and survival outcomes. In 2018 our institution began to evaluate SMART on trial in borderline and locally advanced patients. We previously presented toxicity outcomes for standard fractionated chemoradiation (chemoRT) and SMART groups with acute grade 3+ GI toxicity in 28% vs 11% (P = 0.18) and late toxicity 43% vs 36% (P = 0.77). The purpose of this abstract was to compare overall survival (OS) between chemoRT and SMART. Materials/Methods: In this IRB approved analysis, we retrospectively reviewed 115 consecutive patients from 2017-2020 with locally advanced or borderline resectable pancreatic cancer who were treated with neoadjuvant radiation therapy. Initially all patients received chemoRT to a dose of 50.4 Gy in 28 fractions. In September 2018 we began to investigate SMART (50Gy in 5 fractions) for these patients. OS was evaluated by Kaplan-Meier and log-rank test. Univariate and multivariate analysis was also performed on multiple treatment variables. Results: Of the patients included, 30 received chemoRT and 85 received SMART. Median follow up for the chemoRT group was 32.8 months and for SMART was 14.9 months from last day of RT. Groups did not have significant differences in age, gender, tumor location, or initial CA 19-9. Pancreatectomy was performed in 13.3% vs 18.8% of patients in chemoRT and SMART groups. Per NCCN.1.2021 staging in the chemoRT group 33.3% were borderline (BL), 50% were locally advanced (LA), and 16.7% medically unresectable (MU) as compared to 24.7% BL, 49.4% LA, and 25.9% MU in the SMART group. Mean months of neoadjuvant chemo was slightly higher in the SMART group at 3.6 vs 2.3 months. Patients in the chemoRT arm were 36.7% African American vs 15.3% in the SMART group. When evaluated using Kaplan-Meier and log-rank test there was no difference in OS between groups (P = 0.95). Median OS from last day of RT in chemoRT and SMART groups was 10.7 vs 12.1 months. On univariate and multivariate analyses pancreatectomy was associated with improved OS, and both N2 disease at diagnosis and poor performance status (ECOG 2+) were associated with worse OS. Conclusion: Dose escalated SMART for locally advanced, borderline, and medically inoperable pancreatic cancer shows similar OS to standard fractionated chemoRT at a median 14.9 month follow up in our single institution analysis. With similar toxicity and OS between treatment modalities, SMART may be preferred due to the single week treatment course in a disease with overall very poor prognosis.

Hypertension and Vascular Research

Corey L, Mor G, Matherly L, Jiang J, Yue Y, **Tiwari N**, Hou Z, You Y, Li J, Kim S, Rattan R, Alvero A, and Gogoi R. Metabolomic adaptations associated with chemoresistance in ovarian cancer cell lines. *Int J Gynecol Cancer* 2021; 31(SUPPL 4):A30-A31.

L. Corey, Wayne State University, Oncology, Detroit, United States

Objectives Over 80% of ovarian cancer (OC) patients will experience relapse after an initial response to platinum-based chemotherapy. Acquisition of metabolomic adaptations is thought to be an integral part of chemoresistance, but the relation of these adaptations to chemoresistance is poorly understood. Our aim was to identify the metabolic adaptations that are specifically associated with platinum-resistant (PR) cell lines and its platinum-sensitive (PS) derivatives across multiple OC cell lines. Methods Targeted metabolic analysis evaluating 242 metabolites of the PS A2780, PEO1, and mR182 cell lines was performed along with their respective PR derivatives, C200, PEO4, R182. The group comparison was performed using unpaired t-tests followed by FDR correction. The differentially expressed metabolites were identified using two criteria: FDR ≤ 5% and absolute fold-change ≥ 1.5. The pathway analysis was performed using Metaboanalyst™with the metabolites that have unadjusted p-value ≤5%. Results Many significantly impacted pathways were conserved among the PR cell lines. Compared to the PS counterparts, the PR PEO4, C200, and R182 lines had metabolite concentrations with FC≥1.5 in 29, 44, and 28 measured metabolites, respectively. The top pathways impacted were 'nicotinate and nicotinamide metabolism', 'purine metabolism', and 'phenylalanine, tyrosine, tryptophan biosynthesis'. A global analysis of PS vs PR was performed. The top five significantly impacted pathways were: Arginine biosynthesis, Pyrimidine and Purine metabolism, Phenylalanine, tyrosine and tryptophan biosynthesis' and 'Starch and sucrose metabolism'. Conclusions We identified multiple shared metabolomic pathways among established PR OC cell lines that highlight conserved motifs of PR. These may represent targetable pathways to predict or reverse chemoresistance.

Obstetrics, Gynecology and Women's Health Services

Arun J, **Chavali N**, **Bechler S**, **Klindt D**, and **Vilkins AL**. Hysteroscopic Removal of Foreign Body. *J Minim Invasive Gynecol* 2021; 28(11):S34.

J. Arun, Henry Ford Health System, Detroit, MI, United States

Study Objective: To present a unique case of hysteroscopic removal of retained fetal bone Design: This is a unique video case report of a patient whose infertility workup revealed evidence of suspected retained fetal bone from a remote second trimester abortion. She was counseled and consented for hysteroscopic removal of suspected foreign body. Setting: Operating room. Patients or Participants: There is one patient in this video. She presented for infertility workup with past medical history significant for surgical abortion at 20 weeks gestation, 17 years prior. She was unable to conceive following this procedure. Interventions: Hysteroscopy to remove foreign object. Measurements and Main Results: Ultrasound showed irregular echogenic structure 1.7 by 0.4 cm with dense posterior shadowing in the cervix of uncertain etiology. Differential included retained foreign body such as a fragmented IUD or retained fetal bone from her remote abortion, which was the leading diagnosis. Hysteroscopy was performed for direct visualization and removal of this foreign body. Pathology report confirmed it to be degenerated mature bone. Conclusion: Multiple calcified bony remnants, likely from remote dilation and curettage for termination, were extending through the length of the endocervical canal. Hysteroscopy was utilized to directly visualize and remove these bony remnants to clear the endocervical canal and entrance to uterine cavity.

Obstetrics, Gynecology and Women's Health Services

Cook AE, **Ghanem AI**, **Hijaz M**, **Burmeister C**, and **Elshaikh MA**. Patterns of Recurrence After Adjuvant Vaginal Cuff Brachytherapy and Chemotherapy in Early-Stage Uterine Serous Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e630.

A.E. Cook, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Adjuvant vaginal cuff brachytherapy (VB) and chemotherapy are commonly utilized in women with early-stage uterine serous carcinoma (USC). We sought to characterize predictors of survival endpoints and recurrence patterns in this rare population who received similar adjuvant treatments. Materials/Methods: We queried our prospectively maintained database for patients with 2009 FIGO stages I-II USC who underwent adequate surgical staging at our institution and received adjuvant chemotherapy with carboplatin and paclitaxel along with VB. We excluded women with synchronous malignancies. Overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS)

were assessed by Kaplan-Meier and log-rank tests. Univariate (UVA) and multivariate analyses (MVA) were performed to identify statistically significant predictors of survival endpoints. Variables with $P < 0.1$ on UVA were included in a MVA and any variable with $P < 0.05$ was considered statistically significant. Results: We identified 77 women who met our inclusion criteria who underwent surgical staging between 1991 and 2018. The median follow-up time was 36 months (range 6-125). The median age was 66 years. Of the cohort, 70% were FIGO stage IA, 17% were stage IB, and 13% were stage II. The median number of dissected lymph nodes was 22. There were 10 women (13%) diagnosed with a recurrence with a median time to recurrence of 12.0 months. The main site of initial recurrence was distant in seven patients (70%). For the entire cohort, 5-year OS, DSS, and RFS were 83% (95% Confidence Interval [CI] 0.68-0.91), 92% (95% CI 0.78-0.97), and 83% (95% CI 0.71-0.91), respectively. The sole independent predictor of 5-year DSS was the presence of positive peritoneal cytology (Hazard Ratio 0.03, 95% CI 0.00-0.72, $P = 0.03$). Conclusion: Although 5-year survival outcomes were promising in this cohort, this study suggests that the predominant pattern of relapse in early-stage USC treated with adjuvant chemotherapy and VB is distant, calling for the optimization of systemic therapy. Positive peritoneal cytology is an independent predictor of worse DSS. Multi-institutional pooled analyses are warranted to confirm our study results. Author Disclosure: A.E. Cook: None. A.I. Ghanem: None. M. Hijaz: None. C. Burmeister: None. M.A. Elshaikh: None.

Obstetrics, Gynecology and Women's Health Services

Shukr GH, Shukr M, **Abood J**, and Eisenstein DI. Uterine Sparing Laparoscopic Ablation of Uterine Fibroids: A Survey of Patient's Satisfaction and Treatment Outcomes. *J Minim Invasive Gynecol* 2021; 28(11):S157.

G.H. Shukr, Obstetrics and Gynecology, Minimally Invasive Division, Henry Ford Hospital, West Bloomfield, MI, United States

Study Objective: The primary purpose of this study was to assess the patient's satisfaction with laparoscopic radiofrequency fibroid ablation (Lap-RFA) for the treatment of symptomatic uterine fibroids. We inquired about their quality of life, health state, and overall treatment effects. Design: Survey study. Setting: Community-based tertiary care medical center. Patients or Participants: All patients who underwent a Lap-RFA by a single surgeon between the years of 2012 and 2020. Interventions: laparoscopic radiofrequency fibroid ablation (Lap-RFA). Measurements and Main Results: 48 patients underwent Lap-RFA procedure by the same provider and were mailed surveys for postoperative evaluation. Twenty patients responded, yeilding a 42% response rate. The mean age of the patients was 46 (34-60) years. The average time interval from surgery to survey response was 23 months (1-50). The Uterine fibroid Symptom and Health-Related Quality of Life (UFS-QOL) and the Health State Questionnaire scores are inversely related to outcomes. The UFS-QOL score can range from 37 to 185 with 37 being the optimal outcome. The average UFS-QOL score was found to be 72 (range 37-146). In addition, the Health state questionnaire can range from 5 to 15, and the average score was 6 (range 5-9). On a scale of 1 to 10, 10 representing optimal outcome, the average health rating was 8 (range 5-10). Using the Menorrhagia Impact Questionnaire, seven patients reported improved menses, ten had no change in symptoms, one had worsening symptoms, and two were postmenopausal. Sixteen patients reported some degree of satisfaction with the procedure, while three were dissatisfied with their overall treatment outcomes. Ninety percent of patients would recommend Lap-RFA to a friend. Conclusion: Lap-RFA procedure is an effective uterine-sparing treatment for symptomatic fibroids with good patient satisfaction. The Lap-RFA procedure should be considered when counseling patients about fibroid management options.

Otolaryngology – Head and Neck Surgery

Cook AE, **Modh A**, **Ali H**, **Sheqwara J**, **Chang S**, **Ghanem T**, **Momin S**, **Wu V**, **Tam S**, **Han X**, **Fakhoury L**, **Movsas B**, and **Siddiqui F**. Randomized Phase III, Double-Blind, Placebo-Controlled Study of Prophylactic Gabapentin for the Reduction of Radiation Therapy-Induced Pain During the Treatment of Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S61-S62.

A.E. Cook, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): We sought to determine if prophylactic gabapentin usage in patients undergoing definitive concurrent chemoradiotherapy (chemoRT) for oropharyngeal cancer improves patient-reported quality of life (QOL) metrics, opioid analgesic requirements, and feeding tube (FT) placement. Materials/Methods: This double-blind, randomized phase III study for patients with AJCC 7th ed stage III-IV oropharyngeal squamous cell carcinoma undergoing concurrent chemoRT randomly allocated patients to prophylactic gabapentin (600 mg TID) or placebo, stratified by smoking status. All patients received 70 Gy in 35 fx using IMRT. The primary endpoint was change in Patient-Reported Oral Mucositis Symptom (PROMS) scores from baseline over the study period. Opioid requirements (average over the entire study period and change from baseline, converted to daily morphine equivalents [DME]), FT placement, and other patient-reported QOL metrics (FACT-HN and PRO-CTCAE) were assessed. Questionnaires were administered at baseline, weekly during RT treatments, and at 6-week post-RT follow-up (f/u). Patients were considered compliant if they took at least 12 doses in any given week (self-reported). Repeated measures ANOVA was used to detect differences in PROMS scores and change in opioid use from baseline. Wilcoxon-rank sum tests were used to compare average opioid use, FACT-HN, and PRO-CTCAE scores. Chi-square test was used to compare FT placement. A P value less than 0.05 was considered statistically significant. Results: There were 65 patients enrolled in the study and 7 withdrew consent, leaving 58 patients to be analyzed. Baseline characteristics were well-balanced, and only 1 patient was considered non-compliant. All patients completed RT as planned. No significant difference was found in PROMS scores between the two groups (P = 0.130). FT placement was significantly higher in the gabapentin vs placebo arm (64.3% vs 33.3%, P = 0.003). Of the FTs placed, 96% were Dobhoff tubes. There was no significant difference in terms of average opioid use (median 22.8 DME [IQR 12.8-36.5] vs 15.8 DME [IQR 8.3-32.4], P = 0.412) or change in opioid use (P = 0.818) for gabapentin vs placebo, respectively. For the FACT-HN questionnaire, the only significant difference noted was in the functional well-being index with the gabapentin arm having a significant decrease in scores from baseline to f/u (median -6 [IQR -10 to -1.5] vs -1 [IQR -5.75 to 5], P = 0.017) with lower scores suggesting poorer QOL. PRO-CTCAE scores increased significantly at f/u from baseline for gabapentin vs placebo (median 6 [IQR 3 to 11] vs 1 [IQR -2 to 6.5], P = 0.014) with higher scores suggesting worse QOL. Conclusion: This study suggests that prophylactic gabapentin is not effective in improving pain related to mucositis during chemoRT in patients with oropharyngeal squamous cell carcinoma, and other strategies should be evaluated to minimize opioid usage in this patient population.

Public Health Sciences

Cook AE, **Ghanem AI**, **Hijaz M**, **Burmeister C**, and **Elshaikh MA**. Patterns of Recurrence After Adjuvant Vaginal Cuff Brachytherapy and Chemotherapy in Early-Stage Uterine Serous Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e630.

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0.00-0.72, P = 0.03). Conclusion: Although 5-year survival outcomes were promising in this cohort, this study suggests that the predominant pattern of relapse in early-stage USC treated with adjuvant chemotherapy and VB is distant, calling for the optimization of systemic therapy. Positive peritoneal cytology is an independent predictor of worse DSS. Multi-institutional pooled analyses are warranted to confirm our study results. Author Disclosure: A.E. Cook: None. A.I. Ghanem: None. M. Hijaz: None. C. Burmeister: None. M.A. Elshaikh: None.

Public Health Sciences

Cook AE, **Modh A**, **Ali H**, **Sheqwara J**, **Chang S**, **Ghanem T**, **Momin S**, **Wu V**, **Tam S**, **Han X**, **Fakhoury L**, **Movsas B**, and **Siddiqui F**. Randomized Phase III, Double-Blind, Placebo-Controlled Study of Prophylactic Gabapentin for the Reduction of Radiation Therapy-Induced Pain During the Treatment of Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S61-S62.

A.E. Cook, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): We sought to determine if prophylactic gabapentin usage in patients undergoing definitive concurrent chemoradiotherapy (chemoRT) for oropharyngeal cancer improves patient-reported quality of life (QOL) metrics, opioid analgesic requirements, and feeding tube (FT) placement. Materials/Methods: This double-blind, randomized phase III study for patients with AJCC 7th ed stage III-IV oropharyngeal squamous cell carcinoma undergoing concurrent chemoRT randomly allocated patients to prophylactic gabapentin (600 mg TID) or placebo, stratified by smoking status. All patients received 70 Gy in 35 fx using IMRT. The primary endpoint was change in Patient-Reported Oral Mucositis Symptom (PROMS) scores from baseline over the study period. Opioid requirements (average over the entire study period and change from baseline, converted to daily morphine equivalents [DME]), FT placement, and other patient-reported QOL metrics (FACT-HN and PRO-CTCAE) were assessed. Questionnaires were administered at baseline, weekly during RT treatments, and at 6-week post-RT follow-up (f/u). Patients were considered compliant if they took at least 12 doses in any given week (self-reported). Repeated measures ANOVA was used to detect differences in PROMS scores and change in opioid use from baseline. Wilcoxon-rank sum tests were used to compare average opioid use, FACT-HN, and PRO-CTCAE scores. Chi-square test was used to compare FT placement. A P value less than 0.05 was considered statistically significant. Results: There were 65 patients enrolled in the study and 7 withdrew consent, leaving 58 patients to be analyzed. Baseline characteristics were well-balanced, and only 1 patient was considered non-compliant. All patients completed RT as planned. No significant difference was found in PROMS scores between the two groups (P = 0.130). FT placement was significantly higher in the gabapentin vs placebo arm (64.3% vs 33.3%, P = 0.003). Of the FTs placed, 96% were Dobhoff tubes. There was no significant difference in terms of average opioid use (median 22.8 DME [IQR 12.8-36.5] vs 15.8 DME [IQR 8.3-32.4], P = 0.412) or change in opioid use (P = 0.818) for gabapentin vs placebo, respectively. For the FACT-HN questionnaire, the only significant difference noted was in the functional well-being index with the gabapentin arm having a significant decrease in scores from baseline to f/u (median -6 [IQR -10 to -1.5] vs -1 [IQR -5.75 to 5], P = 0.017) with lower scores suggesting poorer QOL. PRO-CTCAE scores increased significantly at f/u from baseline for gabapentin vs placebo (median 6 [IQR 3 to 11] vs 1 [IQR -2 to 6.5], P = 0.014) with higher scores suggesting worse QOL. Conclusion: This study suggests that prophylactic gabapentin is not effective in improving pain related to mucositis during chemoRT in patients with oropharyngeal squamous cell carcinoma, and other strategies should be evaluated to minimize opioid usage in this patient population.

Public Health Sciences

Liang E, **Kirsch C**, **Gardey V**, **Burmeister C**, **Dragovic J**, and **Parikh PJ**. 90-Day Hospitalization as a Surrogate for Overall Survival in Hepatocellular Carcinoma (HCC) Patients Treated With Magnetic Resonance-Guided Liver Stereotactic Body Radiation Therapy: Results of a Single-Center Retrospective Study. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e53-e54.

E. Liang, Henry Ford Health System, Detroit, MI, United States

Purpose/Objective(s): With the increased utilization of stereotactic body radiation therapy (SBRT) for the management of hepatocellular carcinoma (HCC), it is important to have accurate prognostic factors for

survival to guide treatment management decisions. Here, we examine 90-day hospitalization as a prognostic factor in addition to established staging systems including the albumin-bilirubin (ALBI) grade, Child-Pugh score, and Barcelona Clinic Liver Cancer (BCLC) stage. Materials/Methods: This retrospective single-institution study analyzed 95 patients with HCC treated with SBRT from August 2017 to September 2020. Overall survival (OS) rates were retrospectively analyzed from treatment completion date to death date or last follow-up. Patients were censored from further analysis if subsequent SBRT courses were administered. Patient characteristics, 90-day hospitalization, ALBI grade, Child-Pugh score, and BCLC liver stage were analyzed with the Cox proportional hazard model and log-rank test; any significant factors on univariate analysis were subsequently analyzed in the multivariate analysis. Results: Median overall survival among the entire cohort was 67 months (range 0-38 months). Univariate predictors of overall survival included patient sex ($P = 0.02$), performance status ($P = 0.03$), Child-Pugh score ($P = 0.003$), ALBI grade ($P < 0.0001$), as well as 90-day hospitalization ($P < 0.0001$). However, 90-day hospitalization itself was associated with patient male gender (26.9% vs 7.1%; $P = 0.03$), performance status ($P < 0.0001$), Child-Pugh score ($P = 0.003$), ALBI grade ($P = 0.003$), and BCLC stage ($P = 0.002$). In the multivariate analysis, patient male sex ($P = 0.02$), ALBI grade 3 ($P = 0.05$), and 90-day hospitalization ($P = 0.03$) remained significant. Conclusion: 90-day hospitalization is a significant predictor of overall survival among patients treated with SBRT for HCC. 90-day hospitalization could be used as an early endpoint in trials evaluating liver SBRT.

Public Health Sciences

Schaff EM, **Bagher-Ebadian H**, **Siddiqui F**, **Zhu S**, **Sun Z**, **Ghanem AI**, **Lu M**, **Movsas B**, and **Chetty IJ**. Radiomic Analysis of Primary GTV and CTV for Prediction of Extranodal Extension Using Diagnostic CT Images in Patients With Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e104.

E.M. Schaff, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Prediction of extranodal extension (ENE) status of the involved lymph nodes has been shown to be an important factor in the prognosis and treatment of patients with Oropharyngeal Squamous Cell Carcinomas (OPSCC). Official diagnosis of ENE occurs pathologically at the time of surgery, and typically necessitates aggressive adjuvant treatment with radiation and concurrent chemotherapy. Due to higher toxicity with trimodality therapy, definitive chemoradiation can be a preferred treatment option up front instead of surgery if there is high clinical suspicion of ENE. This study investigates the potential value of radiomic features extracted from pre-treatment primary gross tumor volume (GTV) and clinical target volume (CTV) on diagnostic contrast enhanced Computed Tomography (CE-CT) images for prediction of ENE in patients with OPSCC. Materials/Methods: For this study we identified 26 patients with pathologically confirmed OPSCC who went on to receive surgery and neck nodal dissection. Out of this group 13 were p16 positive, 13 were p16 negative, 7 were pathologic ENE positive, and 19 pathologic ENE negative. We contoured the primary tumor GTV on their pre-surgery CE-CT and added a 1 cm to create the CTV for radiomic analysis. For each patient, two sets of IBSI (Image Biomarker Standardization Initiative) validated radiomic features (N = 192 features from 11 different feature categories) were extracted from primary GTV and CTV on the diagnostic CE-CT images. Levene and Kolmogorov-Smirnov's (KS, $P < 0.05$) tests with confidence level of 95% along with absolute biserial correlation (|BSC|) with a threshold of > 0.2 were used to statistically reveal significant associations between ENE status and radiomics features. The Belsley collinearity diagnostics test was applied on the discriminant radiomic features for removing highly correlated features. Eight different Generalized-Linear Models (GLMs) were trained and tested using each individual feature along with two combined feature sets (combined discriminant features extracted from GTV and CTV). Balanced Accuracy Score (BAS), Positive predictive and negative predictive values (PPV and NPV, respectively) were used to evaluate the performance of the classifiers. Results: Four GTV-based radiomic features and two CTV-based radiomic features (both from textural feature categories) were found to be statistically significant discriminators between the two ENE cohorts. Performances for prediction of the ENE for the two classifiers trained with the combined feature sets were: GTV-based GLM: BAS/PPV/NPV = 0.765/0.724/0.805 and CTV-based GLM: 0.875/0.928/0.822. Results imply that the CTV-based features have greater predictive value compared to GTV-based features for characterization of ENE. Conclusion: This pilot study, albeit subject

to confirmation in a larger patient population, suggests potential for the use of radiomics-based signatures extracted from the primary tumor for prediction of ENE in patients with OPSCC.

Public Health Sciences

Schaff EM, **Kirsch C**, **Gartrelle KJ**, **Li P**, **Khan G**, **Shah R**, **Movsas B**, **Parikh PJ**, **Siddiqui F**, and **Kwon D**. Magnetic Resonance Guided Stereotactic Ablative Radiation Therapy vs. Chemoradiation for Borderline and Locally Advanced Pancreatic Cancer: Single Institution Overall Survival Comparison. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e74-e75.

E.M. Schaff, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Several academic institutions have investigated stereotactic MR guided adaptive radiation therapy (SMART) to safely dose escalate for locally advanced and borderline resectable pancreatic cancer with initial favorable toxicity and survival outcomes. In 2018 our institution began to evaluate SMART on trial in borderline and locally advanced patients. We previously presented toxicity outcomes for standard fractionated chemoradiation (chemoRT) and SMART groups with acute grade 3+ GI toxicity in 28% vs 11% (P = 0.18) and late toxicity 43% vs 36% (P = 0.77). The purpose of this abstract was to compare overall survival (OS) between chemoRT and SMART. Materials/Methods: In this IRB approved analysis, we retrospectively reviewed 115 consecutive patients from 2017-2020 with locally advanced or borderline resectable pancreatic cancer who were treated with neoadjuvant radiation therapy. Initially all patients received chemoRT to a dose of 50.4 Gy in 28 fractions. In September 2018 we began to investigate SMART (50Gy in 5 fractions) for these patients. OS was evaluated by Kaplan-Meier and log-rank test. Univariate and multivariate analysis was also performed on multiple treatment variables. Results: Of the patients included, 30 received chemoRT and 85 received SMART. Median follow up for the chemoRT group was 32.8 months and for SMART was 14.9 months from last day of RT. Groups did not have significant differences in age, gender, tumor location, or initial CA 19-9. Pancreatectomy was performed in 13.3% vs 18.8% of patients in chemoRT and SMART groups. Per NCCN.1.2021 staging in the chemoRT group 33.3% were borderline (BL), 50% were locally advanced (LA), and 16.7% medically unresectable (MU) as compared to 24.7% BL, 49.4% LA, and 25.9% MU in the SMART group. Mean months of neoadjuvant chemo was slightly higher in the SMART group at 3.6 vs 2.3 months. Patients in the chemoRT arm were 36.7% African American vs 15.3% in the SMART group. When evaluated using Kaplan-Meier and log-rank test there was no difference in OS between groups (P = 0.95). Median OS from last day of RT in chemoRT and SMART groups was 10.7 vs 12.1 months. On univariate and multivariate analyses pancreatectomy was associated with improved OS, and both N2 disease at diagnosis and poor performance status (ECOG 2+) were associated with worse OS. Conclusion: Dose escalated SMART for locally advanced, borderline, and medically inoperable pancreatic cancer shows similar OS to standard fractionated chemoRT at a median 14.9 month follow up in our single institution analysis. With similar toxicity and OS between treatment modalities, SMART may be preferred due to the single week treatment course in a disease with overall very poor prognosis.

Public Health Sciences

Shimada S, **Kitajima T**, **Shamaa T**, **Ivanics T**, **Collins KM**, **Rizzari MD**, **Yoshida A**, **Abouljoud MS**, **Lu M**, and **Nagai S**. Improvements in Liver Transplantation Outcomes in Patients with Hepatitis C Virus/HIV Coinfection after the Introduction of Direct-Acting Antiviral Therapies. *J Am Coll Surg* 2021; 233(5):S271-S272.

Introduction: Although liver transplantation (LT) outcomes in patients with hepatitis C virus (HCV) infection have improved after the introduction of direct-acting antivirals (DAAs), their impact on patients with HCV/HIV coinfection has not been evaluated. We aimed to assess the effects of DAAs on post-LT outcomes in patients with HCV/HIV compared with those with HIV or HCV mono-infection. Methods: Using the Organ Procurement and Transplantation Network/United Network for Organ Sharing data, we compared post-LT graft survival in patients with HCV and/or HIV before and after DAAs introduction. Patients were classified into the following eras: era 1 (2008-2012 [pre-DAAs]) and era 2 (2014-2019 [post-DAAs]). Patients who received transplants in 2013 were excluded to allow a washout period of the effect of DAAs. Inverse probability weighting was used to adjust characteristic differences between eras. Analyses considered possible infection by era interactions. Results: A total of 18,053 LT recipients were

identified (HCV/HIV [n = 160]; HCV mono-infection [n = 17,705]; HIV mono-infection [n = 188]). In era 1, the 1-year graft survival rate in the coinfection group was significantly worse than in HCV and HIV mono-infection groups, but no difference was detected in era 2 (Fig. 1). Both HCV/HIV and HCV mono-infection had significant reduction on year-1 graft loss, compared with era 1; hazard ratio 0.25 (95% CI, 0.14 to 0.43) for HIV/HCV and hazard ratio 0.61 (95% CI, 0.57 to 0.65) for HCV (Table 1). Improvement was more prominent in the coinfection group. There was no significant change in patients with HIV mono-infection. Conclusion: After the introduction of DAAs, more significant improvements in post-LT outcomes were observed in patients with coinfection compared with those with HIV or HCV mono-infection.

Radiation Oncology

Bagher-Ebadian H, **Siddiqui F**, **Ghanem AI**, **Zhu S**, **Lu M**, **Movsas B**, and **Chetty IJ**. Superiority of Radiomics Information Compared to Clinical Factors in Characterization of Human Papilloma Virus (HPV) Status in Patients With Oropharyngeal Squamous Cell Carcinomas. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e405-e406.

Purpose/Objective(s): To investigate the potential predictive value of patient clinical factors versus radiomic features extracted from CT images for characterization of Human Papilloma Virus (HPV) status for patients with oropharyngeal squamous cell carcinoma (OPSCC). Materials/Methods: One hundred twenty-eight OPSCC patients with known HPV-status (60-HPV+ and 68-HPV-, confirmed by immunohistochemistry-P16-protein testing) were retrospectively studied. Radiomic features (11 feature-categories) were extracted in 3D from contrast-enhanced (CE)-CT images of gross-tumor-volumes using 'in-house' software (ROdiomX) developed and validated following the image-biomarker-standardization-initiative (IBSI) guidelines. Six categories of clinical factors were investigated: Age-at-Diagnosis, Gender, Total-Charlson comorbidity score, Alcohol-Use, Smoking-History, and T-Stage, according to AJCC 7th-edition. An Elastic Net technique combined with a Generalized-Linear-Model (Lasso-GLM) were applied to perform L1 and L2 regularizations in the radiomic and clinical feature spaces to identify and rank the optimal feature subsets with most representative information for prediction of HPV. Elastic-Net GLM classifiers based on clinical factors only, radiomics only, and combined clinical and radiomics (ensemble/integrated) were constructed using random-permutation-sampling. Tests of significance (One-way ANOVA), average Area-Under-Receiver-Operating-Characteristic (AUC), and Positive and Negative Predictive values (PPV and NPV) were computed to estimate the generalization-error and prediction performance of the classifiers. Results: Five clinical factors, including T-stage, smoking status, and age; and 21 radiomic features, including tumor morphology, textural information, and intensity contrast were found to be statistically significant discriminators between HPV positive and negative cohorts. Performances for prediction of HPV status for the 3 classifiers were: Radiomics Elastic-Net-GLM: AUC/PPV/NPV = 0.799/0.775/0.802; Clinical Elastic-Net-GLM: 0.673/0.738/0.679, and Integrated/Ensemble Elastic-Net-GLM: 0.912/0.884/0.860. Results imply that the radiomics-based classifier significantly outperforms that using clinical factors only, and that the combination of both radiomics and clinical factors yields even higher predictive performance. Conclusion: Albeit subject to confirmation in a larger cohort, this pilot study presents encouraging results in support of the role of radiomic features towards characterization of HPV in patients with OPSCC.

Radiation Oncology

Chapman D, Quinn TJ, and Hamstra DA. Validation of the Combination Gleason Score as an Independent Favorable Prognostic Factor in Prostate Cancer Treated With Dose-Escalated Radiotherapy. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e267.

Purpose/Objective(s): Prognostic factors that alter prostate cancer effect include TNM stage, pre-treatment PSA, Gleason score, and Gleason grade group (2). Of these, Gleason score yields the largest impact on cause-specific survival (CSS) (5). While Gleason score is crucial to predicting outcomes, disparity between biopsy and prostatectomy sample scores is often seen. This can result in Gleason score upgrading (GSU) and downgrading (GSD) at the time of surgery. Phillips et al. explored this phenomenon through combining the lowest and highest Gleason scores at biopsy (ComboGS) and examining how such a factor would impact GSU and prostate cancer specific survival (PCSM). This study aims to validate the Phillips et al. findings via an independent cohort of prostate cancer patients treated with definitive dose-escalated radiation therapy (DE-RT) at a single institution. Materials/Methods: DE-RT

was administered to 2,539 men; 687 men had a ComboGS. We utilized univariate and multivariable analysis to evaluate relapse rates and clinical outcomes. To further ascertain the ComboGS prognostic impact, we employed the Cancer of the Prostate Risk Assessment Score (CAPRA) and the modified CAPRA (mCAPRA). Rates of biochemical event-free survival (bEFS) and distant metastasis-free survival (DMFS) were compared across CAPRA scores, with and without modification, and the prognostic value of the CAPRA scores were compared using Harrel's concordance index (C-index) (12). Results: ComboGS presence in Gleason 7-10 prostate cancer patients generated improved 10-year biochemical event-free survival (bEFS) from 76.6% to 82.4% (HR 0.75, CI 0.59-0.96, P = 0.021), 10-year distant metastasis-free survival (DMFS) from 89.3% to 93.2% (HR 0.57, CI 0.39-0.85, P = 0.005), 10-year PCSM from 93.9% to 97.4% (HR 0.39, CI 0.21-0.7, P = 0.001) and 10-year overall survival (OS) from 65.7% to 75.6% (HR 0.69, CI 0.57-0.83, P < 0.001). Multivariable analysis also supported that ComboGS is protective for biochemical failure (HR 0.64, CI 0.50-0.83, P < 0.001), distant metastasis (HR 0.42, CI 0.28-0.63, P < 0.001), death from prostate cancer (HR 0.32, CI 0.17-0.58, P < 0.001), and overall mortality (HR 0.65, CI 0.54-0.79, P < 0.001). Additionally, adjusting the CAPRA score for ComboGS decreased the risk of biochemical failure (BF) by nearly 30% (HR = 0.70 [95% CI, 0.55-0.88], P = 0.003) and by 50% (HR = 0.54 [95% CI, 0.37-0.80], P = 0.002) for distant metastasis. Conclusion: ComboGS is a useful and readily available independent prognostic factor for all clinical endpoints (biochemical failure, distant metastasis, cancer-specific survival and overall survival). Moreover, the ComboGS can be used in conjunction with the extensively validated CAPRA scoring, to better risk stratify patients being treated with definitive DE-RT and possibly de-escalate therapy for some men with ComboGS 7 disease.

Radiation Oncology

Chuong MD, Clark MA, Henke LE, Kishan AU, Portelance L, **Parikh PJ**, Nagar H, Rosenberg SA, Mehta MP, Abdelrhman TR, Smith AJT, Seung SK, Zaki B, and Mak RH. Patterns of Utilization and Clinical Adoption of 0.35 MR-Guided Radiation Therapy in the United States — Understanding the Transition to Adaptive, Ultra-Hypofractionated Treatments. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e510.

Purpose/Objective(s): Magnetic resonance imaging-guided radiation therapy (MRgRT) utilization is rapidly expanding worldwide, driven by advanced capabilities including continuous intrafraction visualization, automatic triggered beam delivery, and on-table adaptive replanning. Our objective was to describe patterns of 0.35T-MRgRT utilization in the United States (US) among early adopters of this novel technology. Materials/Methods: Anonymized administrative data from all US 0.35T-MRgRT treatment systems were extracted for patients completing treatment from 2014-2020. Detailed treatment information was available for all 0.35T-MR Linac system and some cobalt system patients. Most cobalt patients were included in total only. Results: 17 systems at 16 centers treated 5,733 patients, delivering 40,171 fractions (fractions unavailable for 1,225 cobalt patients), of which 6,244 (15.5%) were adapted. Thirteen centers (81.3%) had treated for > = 1 year, of which 9 treated > 100 patients/year and 6 treated > 150 patients/year. Ultra-hypofractionation (1-5 fractions) was delivered for 72.9% of all patients. The proportion of fractions adapted in patients receiving ultra-hypofractionation was 28.6%, with an average of 3.2 adapted fractions per course. The most commonly treated tumor types were pancreas (20.7%), liver (16.5%), prostate (12.5%), breast (11.5%), and lung (9.4%), respectively, with significantly increased number of fractions delivered from 2018-2020 compared to 2014-2017 for each (pancreas: 5,161 vs. 1,155; liver: 3,597 vs. 921; prostate: 5,795 vs. 1,398; breast: 2,221 vs. 1,876; lung: 2,589 vs. 660). The compound annual growth rate (CAGR) in the number of patients was 59.5%, growing from 111 in 2014 to 1,830 in 2020. Ultra-hypofractionation increased from 31.8% of all treated MR-Linac patients in 2014 to 87.0% in 2020 (n = 1,576/1,811). The proportion of adapted fractions in all patients and ultra-hypofractionation patients increased from 0% in the first two years to 24.3% (n = 3,071/12,639) and 33.8% (n = 2,677/7,911) respectively, by the end of 2020. No patient had adaptive treatment in 2014 although adaptive replanning steadily increased over time. For example, in 2020 vs. 2018 the proportion of adaptive fractions was highest for pancreas (60.6% vs. 50.8%), liver (17.8% vs. 9.9%), and lung (17.8% vs. 1.8%) cancers. Conclusion: This is the first comprehensive study reporting patterns of utilization among early adopters of a 0.35T-MRgRT system in the US. Intrafraction MR guidance, advanced motion management, and increasing adoption of adaptive RT has accelerated a transition to ultra-hypofractionation regimens. MRgRT has been predominantly used to treat abdominal and pelvic tumors, and increasingly with adaptive replanning, which is a radical departure from legacy radiotherapy practices.

Radiation Oncology

Chuong MD, **Kirsch C**, Herrera R, Rubens M, Gungor G, **Schaff EM**, **Dolan J**, **Kim J**, Mittauer KE, Kotecha R, Gutierrez A, **Doemer AJ**, Ugurluer G, **Kwon D**, **Khan G**, Alvarez D, Ucar A, Asbun H, Ozyar E, and **Parikh PJ**. Long-Term Multi-Institutional Outcomes of 5-Fraction Ablative Stereotactic MR-Guided Adaptive Radiation Therapy (SMART) for Inoperable Pancreas Cancer With Median Prescribed Biologically Effective Dose of 100 Gy10. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S147-S148.

Purpose/Objective(s): Randomized trials have shown improved local control (LC) but no overall survival (OS) benefit with the addition of non-ablative radiation therapy (RT) dose compared to chemotherapy (CT) alone for pancreas cancer (PCa). Emerging data suggest that dose-escalated RT may improve LC and OS. A few studies suggest that stereotactic magnetic resonance-guided adaptive RT (SMART) can facilitate the safe delivery of ablative dose for inoperable PCa, although long-term outcomes are not well understood. Materials/Methods: Inoperable PCa patients who received SMART were identified from the RSSearch Registry. Patients with < 3 months (mo.) follow-up after SMART were excluded. LC, progression free survival (PFS), and OS were estimated using the Kaplan-Meier method. LC was evaluated according to RECIST 1.1 criteria. Acute toxicity was considered within 90 days of SMART and evaluated by CTCAE v4 criteria. Results: A total of 148 PCa patients were treated on a 0.35T MR LINAC across 3 institutions between 2018-2020. Median age was 68 years (range 47-91), and 73.6% had ECOG 0-1 performance status. Patients had locally advanced (57.4%), borderline resectable (29.1%), or medically inoperable (13.5%) disease. Median CA19-9 at diagnosis was 202.1 U/mL (range 0.9-21,281). Induction CT was delivered to 89.2% for a median 3.9 mo (range 0.2-11.3); FOLFIRINOX (52.7%) or gemcitabine/nab-paclitaxel (23.4%) were common. Median prescribed RT dose was 50 Gy (range 40-50) in 5 fractions, mostly in consecutive days (96.6%) and in breath hold (95.3%). Median biologically effective dose (BED10) was 100 Gy10. All patients were treated with real-time tissue tracking and automated beam gating without fiducial markers. An elective target volume was rarely used (25%). Pancreaticoduodenectomy was performed in 23% at a median 46 days (range 34-304) after SMART. Median follow-up was 16 mo. from diagnosis for all patients (range, 4-39). Median, 1-year, and 2-year LC was not reached (NR), 94.6%, and 83%, respectively. Median, 1-year, and 2-year PFS was 18 mo., 72%, and 35.9%, respectively. Median, 1-year, and 2-year OS was 26 mo., 82%, and 52.7%, respectively. Acute and late grade 3 toxicity possibly related to SMART occurred in 4.1% and 12.8%, respectively. There was no reported grade 4+ toxicity. Conclusion: To our knowledge, this is the largest reported analysis of 5-fraction SMART for inoperable PCa. These data add to the evidence that ablative radiation dose may improve long-term outcomes including OS. Prospective evaluation of this novel approach is warranted with attention directed at optimizing patient selection, understanding the clinical significance of cumulative dose delivered across all adapted fractions, and assessing treatment response after the delivery of ablative dose.

Radiation Oncology

Coke A, **Gilbert M**, **Hill S**, and **Siddiqui F**. A Multidisciplinary Approach to the Reactive Placement of Nasogastric Feeding Tubes in Clinic During Treatment for Head and Neck Cancer. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e154-e155.

Purpose/Objective(s): Radiation therapy (RT) associated oral mucositis, xerostomia and loss of taste may result in significantly compromised oral intake in patients undergoing treatment for head and neck cancers (HNC). We sought to determine if reactive nasogastric tube (NGT) placement was an effective strategy for nutritional support in these patients and if invasive percutaneous endoscopic gastrostomy (PEG) tube insertion could be avoided. Materials/Methods: This is an IRB- approved study of patients treated for HNC using definitive or adjuvant RT with or without concurrent chemotherapy between June 2017 and December 2020. We evaluated the indications for NGT (Dobhoff) placement, time of placement during the course of RT, patient tolerance of NGT and median duration of NGT placement. In addition, we followed weight loss during treatment, treatment interruptions, and treatment related toxicities. Complications associated with having the NGT, if the NGT needed to be replaced during treatment, and if the patient had any hospitalization during the course of treatment was tracked. The indication for NGT placement is weight loss > 10% of baseline during the course of treatment, most often due to dysphagia and/or odynophagia unrelieved by pain medication. NGT placement is done in the radiation oncology

outpatient clinic by the attending physician and/or nurse practitioner. Results: Of the 441 patients treated during the time period of this study, 47 required reactive NGT placement for nutritional support. Patients included 40 with primary oropharynx, 3 oral cavity, 2 larynx, 1 nasopharyngeal, and 1 unknown. Chemotherapy was given concurrently with radiation in 87.2% (41/47) patients. The median time of NGT placement was during week 5.0 of the 6–7-week course of RT. The median percentage weight loss from baseline to the date of NGT placement was 12.9%. The median duration of NGT placement was 29 days (range, 5 to 151 days). There were no serious medical complications associated with having the NGT in place during treatment. 27.6% (13/47) of patients had the NGT dislodged or displaced and needed replacement. 4.3% (2/47) of patients had the NGT replaced due to clogging. 38.3% (18/47) of patients with an NGT had to be hospitalized during the course of RT, with the predominant symptoms being failure to thrive 22.2% (4/18) and nausea/vomiting 22.2% (4/18). 6.4% (3/47) of patients requested removal of the NGT due to local irritation. 76.6% (36/47) of patients did not require further nutritional support with the placement of a percutaneous endoscopic gastrostomy (PEG) tube. Conclusion: This study indicates clinic placement of an NGT for patients receiving RT for head and neck cancer is a safe and effective way to maintain nutrition during treatment. The rate of weight loss decreased after the patient had an NGT placed. The placement procedure is well tolerated and there were no complications associated with having the NGT during treatment. PEG tube insertion was avoided in 76.6% of the patients.

Radiation Oncology

Cook AE, **Ghanem AI**, **Hijaz M**, **Burmeister C**, and **Elshaikh MA**. Patterns of Recurrence After Adjuvant Vaginal Cuff Brachytherapy and Chemotherapy in Early-Stage Uterine Serous Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e630.

Purpose/Objective(s): Adjuvant vaginal cuff brachytherapy (VB) and chemotherapy are commonly utilized in women with early-stage uterine serous carcinoma (USC). We sought to characterize predictors of survival endpoints and recurrence patterns in this rare population who received similar adjuvant treatments. Materials/Methods: We queried our prospectively maintained database for patients with 2009 FIGO stages I-II USC who underwent adequate surgical staging at our institution and received adjuvant chemotherapy with carboplatin and paclitaxel along with VB. We excluded women with synchronous malignancies. Overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) were assessed by Kaplan-Meier and log-rank tests. Univariate (UVA) and multivariate analyses (MVA) were performed to identify statistically significant predictors of survival endpoints. Variables with $P < 0.1$ on UVA were included in a MVA and any variable with $P < 0.05$ was considered statistically significant. Results: We identified 77 women who met our inclusion criteria who underwent surgical staging between 1991 and 2018. The median follow-up time was 36 months (range 6-125). The median age was 66 years. Of the cohort, 70% were FIGO stage IA, 17% were stage IB, and 13% were stage II. The median number of dissected lymph nodes was 22. There were 10 women (13%) diagnosed with a recurrence with a median time to recurrence of 12.0 months. The main site of initial recurrence was distant in seven patients (70%). For the entire cohort, 5-year OS, DSS, and RFS were 83% (95% Confidence Interval [CI] 0.68-0.91), 92% (95% CI 0.78-0.97), and 83% (95% CI 0.71-0.91), respectively. The sole independent predictor of 5-year DSS was the presence of positive peritoneal cytology (Hazard Ratio 0.03, 95% CI 0.00-0.72, $P = 0.03$). Conclusion: Although 5-year survival outcomes were promising in this cohort, this study suggests that the predominant pattern of relapse in early-stage USC treated with adjuvant chemotherapy and VB is distant, calling for the optimization of systemic therapy. Positive peritoneal cytology is an independent predictor of worse DSS. Multi-institutional pooled analyses are warranted to confirm our study results. Author Disclosure: A.E. Cook: None. A.I. Ghanem: None. M. Hijaz: None. C. Burmeister: None. M.A. Elshaikh: None.

Radiation Oncology

Cook AE, **Modh A**, **Ali H**, **Sheqwara J**, **Chang S**, **Ghanem T**, **Momin S**, **Wu V**, **Tam S**, **Han X**, **Fakhoury L**, **Movsas B**, and **Siddiqui F**. Randomized Phase III, Double-Blind, Placebo-Controlled Study of Prophylactic Gabapentin for the Reduction of Radiation Therapy-Induced Pain During the Treatment of Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S61-S62.

Purpose/Objective(s): We sought to determine if prophylactic gabapentin usage in patients undergoing definitive concurrent chemoradiotherapy (chemoRT) for oropharyngeal cancer improves patient-reported

quality of life (QOL) metrics, opioid analgesic requirements, and feeding tube (FT) placement. Materials/Methods: This double-blind, randomized phase III study for patients with AJCC 7th ed stage III-IV oropharyngeal squamous cell carcinoma undergoing concurrent chemoRT randomly allocated patients to prophylactic gabapentin (600 mg TID) or placebo, stratified by smoking status. All patients received 70 Gy in 35 fx using IMRT. The primary endpoint was change in Patient-Reported Oral Mucositis Symptom (PROMS) scores from baseline over the study period. Opioid requirements (average over the entire study period and change from baseline, converted to daily morphine equivalents [DME]), FT placement, and other patient-reported QOL metrics (FACT-HN and PRO-CTCAE) were assessed. Questionnaires were administered at baseline, weekly during RT treatments, and at 6-week post-RT follow-up (f/u). Patients were considered compliant if they took at least 12 doses in any given week (self-reported). Repeated measures ANOVA was used to detect differences in PROMS scores and change in opioid use from baseline. Wilcoxon-rank sum tests were used to compare average opioid use, FACT-HN, and PRO-CTCAE scores. Chi-square test was used to compare FT placement. A P value less than 0.05 was considered statistically significant. Results: There were 65 patients enrolled in the study and 7 withdrew consent, leaving 58 patients to be analyzed. Baseline characteristics were well-balanced, and only 1 patient was considered non-compliant. All patients completed RT as planned. No significant difference was found in PROMS scores between the two groups (P = 0.130). FT placement was significantly higher in the gabapentin vs placebo arm (64.3% vs 33.3%, P = 0.003). Of the FTs placed, 96% were Dobhoff tubes. There was no significant difference in terms of average opioid use (median 22.8 DME [IQR 12.8-36.5] vs 15.8 DME [IQR 8.3-32.4], P = 0.412) or change in opioid use (P = 0.818) for gabapentin vs placebo, respectively. For the FACT-HN questionnaire, the only significant difference noted was in the functional well-being index with the gabapentin arm having a significant decrease in scores from baseline to f/u (median -6 [IQR -10 to -1.5] vs -1 [IQR -5.75 to 5], P = 0.017) with lower scores suggesting poorer QOL. PRO-CTCAE scores increased significantly at f/u from baseline for gabapentin vs placebo (median 6 [IQR 3 to 11] vs 1 [IQR -2 to 6.5], P = 0.014) with higher scores suggesting worse QOL. Conclusion: This study suggests that prophylactic gabapentin is not effective in improving pain related to mucositis during chemoRT in patients with oropharyngeal squamous cell carcinoma, and other strategies should be evaluated to minimize opioid usage in this patient population.

Radiation Oncology

Dai Z, Jambor I, Taimen P, **Pantelic M**, **Elshaikh MA**, **Dabaja A**, **Rogers C**, Ettala O, Boström P, Aronen H, Merisaari H, and **Wen N**. Accurate Prostate Cancer Detection and Segmentation Using Non-Local Mask R-CNN With Histopathological Ground Truth. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S45.

Purpose/Objective(s): We aim to develop deep learning (DL) models to accurately detect and segment intraprostatic lesions (IL) on biparametric MRI (bp-MRI). Materials/Methods: Three patient cohorts with ground truth IL delineated on different modalities were collected. 158 patients from two datasets had suspicious ILs delineated based on bp-MRI: 97 patients were from PROSTATEx-2 Challenge with biopsy result independent from bp-MRI based delineation, 61 patients were from IMPROD clinical Trial with biopsy done for each delineation; 64 patients from IMPROD clinical Trial had ILs identified and delineated by using whole mount prostatectomy specimen sections as reference standard; 40 private patients were unlabeled. We proposed a non-local Mask R-CNN to improve segmentation accuracy by addressing the imperfect registration issue between MRI modalities. We also proposed to post aggregate 2D predictions to estimate IL volumes within the whole prostatic gland and keep top-5 3D predictions for each patient. In order to explore the small dataset problem, we employed different learning techniques including transfer learning and semi-supervised learning with pseudo labelling. We experimented with two label selection strategies to see how they affected model performance. The first strategy kept only one prediction by referring to biopsy result, in order to minimize false positives; while the second strategy kept all top-5 predictions. 3D top-5 detection rate, dice similarity coefficient (DSC), 95 percentile Hausdorff Distance (95 HD, mm) and true positive ratio (TPR) were our evaluation metrics. We compared DL model prediction with prostatectomy-based ground truth delineation to accurately evaluate the boundary and malignancy level. We separately evaluated ILs of all Gleason Grade Group (GGG) and clinically significant ILs (GGG > 2). Results: Main results are summarized in Table 1. Conclusion: Our proposed method demonstrates state-of-art performance in the detection and segmentation of ILs and shows great effectiveness for clinically significant ILs.

Radiation Oncology

Herr DJ, Hochstedler K, Yin H, Dess RT, Matuszak MM, Grubb M, Dominello MM, **Movsas B**, Kestin LL, Bergsma DP, Dragovic AF, Grills IS, Hayman JA, Paximadis PA, Schipper M, and Jolly S. Effect of Education and Standardization of Cardiac Dose Constraints on Heart Dose in Lung Cancer Patients Receiving Definitive Radiation Therapy Across a Statewide Consortium. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S126.

Purpose/Objective(s): Cardiac radiation exposure is associated with an increased rate of adverse cardiac events in patients receiving radiation therapy for locally advanced non-small cell lung carcinoma (NSCLC). Previous analysis of practice patterns within the statewide Michigan Radiation Oncology Quality Consortium (MROQC) revealed 1 in 4 patients received a mean heart dose > 20 Gy and significant heterogeneity existed among treatment centers in using cardiac dose constraints. The purpose of this study is to analyze the effect of education and initiation of standardized cardiac dose constraints on heart dose across a statewide consortium. Materials/Methods: From 2012 to 2020, 1604 patients from 27 academic and community centers who received radiation therapy for locally advanced NSCLC were included in this analysis. Dosimetric endpoints including mean heart dose (MHD), mean lung dose, and mean esophagus dose were calculated using data from dose-volume histograms. These dose metrics were grouped by year of treatment initiation for all patients. Education regarding data for cardiac dose constraints was discussed in small lung cancer working group meetings and consortium-wide starting in 2016. This was followed in 2018 by implementation of a quality metric requiring mean heart dose < 20 Gy while maintaining dose coverage (D95) to the tumor. Dose metrics were compared before (2012-2016) and after (2017-2019) initiation of interventions targeting cardiac constraints. Statistical analysis was performed using the Wilcoxon Rank Sum test. Results: Following education and implementation of the heart dose performance metric, mean MHD declined from an average of 12.2 Gy pre-intervention to 10.4 Gy post-intervention, and the percentage of patients receiving MHD > 20 Gy reduced by half. (Table). Mean lung dose and mean esophagus dose did not increase, and tumor coverage remained unchanged. Conclusion: Education and implementation of a standardized cardiac dose quality measure across a statewide consortium was associated with a reduction of mean heart dose in patients receiving radiation therapy for locally advanced NSCLC. These dose reductions were achieved without sacrificing tumor coverage, increasing mean lung dose or mean esophagus dose. Analysis of the clinical ramifications of the reduction in cardiac doses is ongoing.

Radiation Oncology

Higgins KA, Hu C, Stinchcombe TE, Jabbour SK, Kozono DE, Owonikoko TK, **Movsas B**, Ritter TA, Xiao C, Williams TM, Welsh JW, Simko J, Wang X, Mohindra NA, Hsu CC, and Bradley JD. NRG Oncology/Alliance LU005: A Phase II/III Randomized Study of Chemoradiation vs. Chemoradiation Plus Atezolizumab in Limited Stage Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e470-e471.

Purpose/Objective(s): Clinical outcomes for limited stage small cell lung cancer (LS-SCLC) remain suboptimal. Standard of care chemoradiation with platinum/etoposide and thoracic radiation to 45 Gy delivered twice daily followed by prophylactic cranial irradiation yields a median overall survival of 30 months. LU005 is a randomized phase II/III trial designed to test the addition of atezolizumab to concurrent chemoradiation. Materials/Methods: Patients with LS-SCLC (Tx-T4, N0-N3, M0) are randomly assigned in a 1:1 ratio to either standard chemoradiation, consisting of thoracic radiation (45 Gy twice daily or 66 Gy daily) with concurrent platinum/etoposide chemotherapy, or the experimental arm, consisting of the same chemoradiation regimen plus the addition of atezolizumab delivered concurrently with thoracic radiation, every 3 weeks for 12 months duration. Thoracic radiation begins with the second cycle of chemotherapy in both treatment arms. Stratification variables include radiation schedule (once daily vs. twice daily), chemotherapy (cisplatin vs. carboplatin), gender, and performance status (PS 0/1 vs. 2). Prophylactic cranial radiation is recommended for patients who have a response to treatment. The phase II primary endpoint is progression free survival (PFS) and the phase III primary endpoint is overall survival (OS). The overall sample size for phase II/III will be 506. Secondary endpoints include objective response rates, local control, distant metastases free, and quality of life. Correlative studies will include blood and tissue based tumor mutational burden analysis, with the hypothesis that higher mutational burden will predict for improved PFS in the experimental arm. Results: As of 3/01/2021, 374 sites are

approved to enroll patients. Two-hundred patients have been accrued. Current enrollment is ahead of projected accrual. Conclusion: LU005 is a randomized II/III trial testing the addition of atezolizumab to standard chemoradiation for LS-SCLC. Accrual remains robust in spite of the ongoing COVID 19 pandemic. Funding: This project was supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), U24CA180803 (IROC) from the National Cancer Institute (NCI) and Genentech.

Radiation Oncology

Hoffe S, Kim DW, Malafa M, Costello J, Aguilera TA, Beg SM, **Parikh PJ**, Herman JM, Terry K, Holmlund J, and Moser EC. GRECO-2: A Randomized, Phase 2 Study of Stereotactic Body Radiation Therapy (SBRT) in Combination with GC4711 in the Treatment of Unresectable or Borderline Resectable Nonmetastatic Pancreatic Cancer (PC). *Int J Radiat Oncol Biol Phys* 2021; 111(3):e44-e45.

Purpose/Objective(s): New therapeutic approaches are needed to improve survival in PC. The GRECO-2 study is designed to examine survival benefit of adding GC4711 to multi-modality treatment in selected patients, responsive to first line (m)FOLFIRINOX. While systemic treatment of PC has improved, rates of surgical resection - considered optimum treatment - remain low due to toxicity and disease progression during induction chemotherapy. SBRT is practiced enhancing resection rates and has shifted to higher dose delivery (Mellon 2015, Colbert 2018), but timing and appropriate patient selection are under constant debate. SBRT delivery over 50Gy exhibits superior cell killing compared to conventionally RT but carries potential GI toxicity risk (Zhong 2017). GC4711 is a selective superoxide dismutase mimetic that converts superoxide to hydrogen peroxide. As radiation response modifiers, dismutase mimetics have the potential to increase tumor control without compromising radiation safety (Sishc, AACR 2019). GC4711 consistently augmented the anti-tumor activity of SBRT in PC experimental xenograft mouse models. In a pilot Phase 1/2 trial (GC4419-101), subjects with locally advanced PC were randomized to receive SBRT with a selective dismutase mimetic or placebo. This pilot trial has demonstrated acceptable safety with SBRT (5 × 10-11Gy), as well as apparent improvements in survival, surgical resection, locoregional control, and time to distant metastases. Altogether, these data support the hypothesis that GC4711 may improve tumor outcomes and the benefit-risk ratio of 5-fraction SBRT delivering 50Gy by improving efficacy without increasing GI toxicity. Materials/Methods: GRECO-2 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study (NCT04698915) to determine the effect on the overall survival of adding GC4711 to SBRT following 4 months of chemotherapy in subjects with unresectable or borderline nonmetastatic PC. Approximately 160 subjects will be randomized (20 sites) to receive GC4711 100 mg or placebo IV infusion over 15 min, prior to each SBRT (5×10Gy). All subjects will then complete 2 additional months of adjuvant chemotherapy. Subjects judged operable will be operated within 8 weeks after SBRT. Secondary endpoints address resection rates, local and distant disease progression, and safety, while exploratory studies include ctDNA, immune profiling, PRO-CTCAE, CA19.9 normalization, and radiomics. Results: For trial progress, see NCT04698915. Conclusion: GC4711 may improve the benefit-risk ratio of 5-fraction SBRT and drive survival benefit of local treatment of chemotherapy responsive PC patients.

Radiation Oncology

Huang Y, **Liang E**, **Schaff EM**, **Zhao B**, **Snyder K**, **Wen N**, **Chetty IJ**, **Shah MM**, and **Siddiqui S**. Impact of MRI Sequence Resolution for Target Volume Definition in Stereotactic Radiosurgery. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e127-e128.

Purpose/Objective(s): MRI is a standard image modality in cranial radiosurgery (SRS) for defining the target volume. There is disparity with different MRI sequences however due to differences in acquisition resolution, which can directly impact accuracy of target segmentation. Here we acquired MRI using different sequences on phantoms to evaluate the effect on volume delineation in the context of cranial SRS. Materials/Methods: Four different T1-weight MR pulse sequences were included: (1) SE5mm: axial and coronal Spin Echo (SE) 2D acquisition with 0.4 × 0.4 mm2 in-plane resolution and 5 mm cross-plane; (1) SE3mm: axial and coronal SE with 0.5 × 0.5 mm2 in-plane and 3 mm cross-plane; (3) TFE: gradient echo 3D acquisition with 0.92 × 0.92 mm2 in axial plane and 1.25 mm cross-plane; (4) BRAVO: gradient echo 3D with 0.4 × 0.4 mm2 in axial plane and 0.5 mm cross-plane. Four phantoms with different shape and volume (0.54 to 25 cm3) were imaged, resulting in 16 sets of MRIs. Four radiation oncologists

provided contours on individual sets of MRIs. All observer contours were compared with ground truth, which was defined on CT image according to the absolute dimensions of the phantom structures. Dice coefficients (DSC), Hausdorff distance (MaxHD, MeanHD, σHD) as well as ratio between reconstructed and true volume (Ratiovol) were evaluated between observer and ground truth contours. A two-sided signed-rank test was performed to determine whether differences were statistically significant. Results: The comparison to ground truth as a function of MR sequence is presented in the Table. All indices improved as the MR resolution increased from SE5mm to BRAVO. All differences, with the exception of Ratiovol between SE3mm and TFE, were statistically significant ($P < 0.01$). Inter-observer variation which must be considered was likely due to: (1) differences in user window/level preferences and related impact on visualization of target boundaries; (2) discrepancies in visualization at the superior/inferior aspect of the target. The first factor leads to systematic over- or under-estimation of the target volume. The second factor affects only SE5mm and SE3mm and leads to over- or under-estimation at superior/inferior aspect of the target. Both factors have ramification in clinical SRS treatment planning. Conclusion: Significant improvement in target definition was observed as the MR image resolution improved. Results imply that the highest resolution 3D MR sequences should be used to minimize potential errors in target definition, and multi-slice 2D sequence should be avoided.

Radiation Oncology

Krauss DJ, Karrison TG, Martinez AA, Morton G, Yan D, Bruner DW, **Movsas B**, **Elshaikh MA**, Citrin DE, Hershatter B, Michalski JM, Efstathiou JA, Currey AD, Kavadi VS, Cury F, Lock MI, Raben A, and Sandler HM. Dose Escalated Radiotherapy Alone or in Combination With Short-Term Androgen Suppression for Intermediate Risk Prostate Cancer: Outcomes From the NRG Oncology/RTOG 0815 Randomized Trial. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S1.

Purpose/Objective(s): Androgen suppression can improve outcomes when added to radiotherapy (RT) for intermediate risk prostate cancer, but no study to date has reported its utility in the context of contemporary, dose-escalated RT. Herein, the clinical outcomes of a phase III prospective trial evaluating the utility of total androgen suppression (TAS) combined with dose-escalated RT for patients with intermediate risk prostate cancer are reported. Materials/Methods: Eligible patients had intermediate risk prostate cancer defined as harboring ≥ 1 of the following risk factors: clinical stage T2b-T2c, Gleason score 7, or PSA value > 10 and ≤ 20 ng/mL. Patients with all three risk factors and ≥ 50% of biopsy cores positive were ineligible. After stratification by number of intermediate risk factors (single vs. multiple), RT boost modality, and baseline comorbidity (ACE-27 comorbidity index ≥ vs. < grade 2), patients were randomized to dose-escalated RT alone (Arm 1) or combined with TAS (Arm 2) consisting of LHRH agonist/antagonist in combination with oral antiandrogen for a duration of 6 months. Permitted RT modalities were external beam radiotherapy (EBRT) alone to total dose 79.2 Gy or EBRT (45 Gy) combined with LDR or HDR brachytherapy boost. Pelvic nodal RT was not permitted. Under a 1-sided significance level of 0.025 and 85% power, the study was designed to detect an improvement in the 5-year overall survival rate from 90% (Arm 1) to 93.3% (Arm 2). Patient reported quality of life outcomes were collected and are reported in another abstract. Results: The study completed its accrual objective. Between 2009 and 2016, 1538 patients were randomized. There were 750 eligible patients on Arm 1 and 742 on Arm 2 comprising the modified intent-to-treat population. 67% had a single intermediate risk factor. 88% were treated with EBRT with the remainder receiving EBRT plus brachytherapy boost. 33% had an ACE-27 score ≥ grade 2. With a median follow up of 6.2 years, 219 deaths occurred, 119 in Arm 1 and 100 in Arm 2, yielding 5-year overall survival estimates of 90% vs. 91%, respectively [HR 0.85 (95% CI 0.65-1.11); $P = 0.22$]. 193 patients experienced PSA failure, 125 in Arm 1 and 68 in Arm 2 [HR 0.52 (0.39-0.70); $P < 0.001$]. 35 patients developed distant metastases, 28 in Arm 1 and 7 in Arm 2 [HR 0.25 (0.11-0.57); $P < 0.001$]. 11 deaths were attributed to prostate cancer, 10 in Arm 1 and 1 in Arm 2 [HR 0.10 (0.01-0.80); $P = 0.007$]. One hundred three acute grade ≥ 3 adverse events occurred, 17 (2.3%) in Arm 1 and 86 (17.5%) in Arm 2 ($P < 0.001$). The cumulative incidence of late grade ≥ 3 adverse events was 16.2% in Arm 1 and 17.5% in Arm 2 ($P = 0.27$). Conclusion: While the addition of TAS to dose-escalated RT did not improve overall survival for men with intermediate risk prostate cancer, significant improvements in rates of metastases, deaths due to prostate cancer, and PSA failures support the continued use of combination dose-escalated RT and TAS. Benefits will need to be weighed against the increased risk of adverse events and the patient reported outcomes analysis.

Radiation Oncology

Liang E, **Kirsch C**, **Gardey V**, **Burmeister C**, **Dragovic J**, and **Parikh PJ**. 90-Day Hospitalization as a Surrogate for Overall Survival in Hepatocellular Carcinoma (HCC) Patients Treated With Magnetic Resonance-Guided Liver Stereotactic Body Radiation Therapy: Results of a Single-Center Retrospective Study. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e53-e54.

Purpose/Objective(s): With the increased utilization of stereotactic body radiation therapy (SBRT) for the management of hepatocellular carcinoma (HCC), it is important to have accurate prognostic factors for survival to guide treatment management decisions. Here, we examine 90-day hospitalization as a prognostic factor in addition to established staging systems including the albumin-bilirubin (ALBI) grade, Child-Pugh score, and Barcelona Clinic Liver Cancer (BCLC) stage. Materials/Methods: This retrospective single-institution study analyzed 95 patients with HCC treated with SBRT from August 2017 to September 2020. Overall survival (OS) rates were retrospectively analyzed from treatment completion date to death date or last follow-up. Patients were censored from further analysis if subsequent SBRT courses were administered. Patient characteristics, 90-day hospitalization, ALBI grade, Child-Pugh score, and BCLC liver stage were analyzed with the Cox proportional hazard model and log-rank test; any significant factors on univariate analysis were subsequently analyzed in the multivariate analysis. Results: Median overall survival among the entire cohort was 67 months (range 0-38 months). Univariate predictors of overall survival included patient sex ($P = 0.02$), performance status ($P = 0.03$), Child-Pugh score ($P = 0.003$), ALBI grade ($P < 0.0001$), as well as 90-day hospitalization ($P < 0.0001$). However, 90-day hospitalization itself was associated with patient male gender (26.9% vs 7.1%; $P = 0.03$), performance status ($P < 0.0001$), Child-Pugh score ($P = 0.003$), ALBI grade ($P = 0.003$), and BCLC stage ($P = 0.002$). In the multivariate analysis, patient male sex ($P = 0.02$), ALBI grade 3 ($P = 0.05$), and 90-day hospitalization ($P = 0.03$) remained significant. Conclusion: 90-day hospitalization is a significant predictor of overall survival among patients treated with SBRT for HCC. 90-day hospitalization could be used as an early endpoint in trials evaluating liver SBRT.

Radiation Oncology

Moskalenko M, Kim H, Chin RI, Roy A, Badiyan SN, Bauer P, Fakhoury K, Henke LE, Herter W, Lieu C, Moyer AM, Mutch M, **Parikh PJ**, Pedersen K, Schefter T, Silviera M, Srivastava G, Vogel JD, Chapman B, and Olsen JR. Multi-Institutional Comparison of SC-TNT and LC-TNT for Rectal Cancer Non-Operative Management. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S104.

Purpose/Objective(s): Recent data support the use of total neoadjuvant therapy (TNT) for treatment of locally advanced rectal cancer (LARC), although the optimal TNT regimen and therapy sequence is unclear for non-operative management (NOM). We performed a multi-institutional comparison of short-course radiation (SCRT) followed by consolidation chemotherapy (SC-TNT) versus long-course chemoradiation (CRT) preceded by induction chemotherapy (LC-TNT), after adoption of NOM at both institutions. Materials/Methods: The records of 187 patients with cT2-4N0-2 rectal cancer treated between 2016-2020 with TNT at two academic institutions were reviewed under an IRB-approved protocol. The SC-TNT cohort (institution 1) included 85 patients treated with SCRT (25-30 Gy in 5 fx) followed by FOLFOX/CAPOX (n = 82) or capecitabine (n = 3). The LC-TNT cohort (institution 2) included 102 patients treated with FOLFOX/CAPOX followed by CRT (45-56 Gy at 1.8-2 Gy/fx) with concurrent fluoropyrimidine-based chemotherapy. Patients with a clinical complete response (cCR) were offered NOM. The rates of cCR were compared between SC- and LC-TNT. Disease-free survival (DFS) was compared using the log-rank test. To account for any differences in NOM selection between institutions, local-only tumor regrowth was censored from DFS if salvaged with R0 resection, and the overall complete response (CR) rate, defined as cCR + pCR rate for patients undergoing surgery, was assessed. Multivariate analysis (MVA) was performed with logistic and Cox regression to determine factors associated with CR and DFS, respectively. Results: The median age at diagnosis was 60 and 54 years for SC-TNT and LC-TNT cohorts, respectively ($P = 0.002$). All other characteristics including performance status, tumor location, and clinical stage were balanced. The median duration of neoadjuvant FOLFOX/CAPOX chemotherapy was 105 vs 98 days for the SC-TNT and LC-TNT cohorts, respectively ($P = 0.001$). The median follow-up was 27 months. The cCR rate was higher in the SC-TNT cohort (44/85, 52.8% vs 21/102, 20.6%, $P < 0.001$), with a trend for improved CR rate for SC-TNT (54.1% vs 40.2%, $P = 0.057$). On MVA, use of SC-TNT was associated with improved CR (HR = 2.24, 95% CI: 1.13-

4.45, P = 0.021). Among patients undergoing NOM, 33/39 patients (84.6%) in the SC-TNT group and 10/17 patients (58.8%) in the LC-TNT group (P = 0.27) were free from local recurrence at 1 year. Two-year DFS was 93.4% and 95.4% for the SC-TNT and LC-TNT cohorts with improved DFS on log-rank test for LC-TNT (P = 0.023), but no DFS difference on MVA between SC-TNT and LC-TNT (HR = 2.29, 95% CI: 0.8-6.51, P = 0.121). Conclusion: SC-TNT demonstrated a greater rate of cCR compared to LC-TNT, without DFS difference on MVA. Although future studies are warranted to compare SC-TNT with a CRT and consolidative chemotherapy TNT approach, our data support SC-TNT as a suitable regimen for LARC NOM.

Radiation Oncology

Movsas B, Rodgers J, **Elshaikh MA**, Martinez AA, Morton G, Krauss DJ, Yan D, Citrin DE, Hershatter B, Michalski JM, Ellis RJ, Kavadi VS, Gore EM, Gustafson GS, Schulz CA, Velker V, Olson AC, Karrison TG, Sandler HM, and Bruner DW. Dose Escalated Radiotherapy (RT) Alone or in Combination With Short-Term Total Androgen Suppression (TAS) for Intermediate Risk Prostate Cancer: Patient Reported Outcomes (PROs) From the NRG Oncology/RTOG 0815 Randomized Trial. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S3.

Purpose/Objective(s): To report the PROs of a phase III randomized trial evaluating TAS combined with dose-escalated RT for patients with intermediate risk prostate cancer. Materials/Methods: Eligible patients had intermediate risk prostate cancer defined as harboring ≥ 1 of these risk factors: clinical stage T2b-T2c, Gleason score 7, or PSA > 10 to ≤ 20 ng/mL. Patients were randomized to dose-escalated RT alone (Arm 1) or RT plus TAS (Arm 2) consisting of LHRH agonist/antagonist with oral antiandrogen for 6 months. Validated PROs included the Expanded Prostate Cancer Index Composite (EPIC-50) and Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue short form. PRO change scores, calculated for each patient as the follow-up score minus baseline score (at end of RT, 6, 12, and 60 months from start of RT) were compared between treatment arms using a two-sample t test. An effect size (ES) of 0.50 SD (standard deviation) of the baseline measure was considered clinically meaningful. For the PRO sample size, 200 patients per arm would provide 90% statistical power to detect an ES < 0.50 if the completion rate was only 60%. Mixed effect regression models were also utilized. Clinical outcomes are reported in a separate abstract. Results: Of the 402 initial planned subset of trial patients who completed baseline PROs, PRO compliance was approximately 96%, 89%, 86% and 87% at end of RT, 6, 12 and 60 months, respectively. There were no significant differences between these 402 patients and the remaining patients on this trial with respect to age, race, performance status, # risk factors, or comorbidity score. While EPIC urinary and bowel scores decreased significantly by the end of RT in both arms, no clinically meaningful differences between arms were detected over time. For the EPIC hormonal and sexual domains, however, there were clinically meaningful differences between the two arms with greater (P < 0.0001) deficits in the RT + TAS arm. These differences improved over time, with ~50% resolution by one year after treatment and no clinically meaningful differences by 5 years between arms. PROMIS-fatigue scores increased from baseline in both arms and were significantly higher in arm 2 at the end of RT (P = 0.016), though slightly lower at 12 and 60 months. Conclusion: The addition of TAS to dose-escalated RT demonstrated significant clinically meaningful declines in the EPIC hormonal and sexual domains, and increases in the PROMIS-fatigue scores, compared to RT alone. These scores gradually improved over time, with no clinically meaningful differences between arms in fatigue by one year, or in hormonal and sexual domains by 5 years. Beyond the clinical outcomes, these PRO results directly from patients provide added value to help patients make informed decisions among treatment options.

Radiation Oncology

Raldow A, Siker ML, Bonner JA, Chen Y, Liu FF, Metz JM, **Movsas B**, Potters L, Schultz CJ, Sanders T, Wang X, Steinberg ML, and Jagsi R. Assessment of Differences in Academic Rank and Salary by Gender and Race Among United States Academic Radiation Oncologists. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e338-e339.

Purpose/Objective(s): We sought to describe the academic radiation oncology workforce including any contemporary differences in salary and rank by sex and race/ethnicity. Materials/Methods: We led a retrospective cohort study using data from the SCAROP 2018 Financial Survey, which included items

related to department characteristics (region of country, institutional funding, and size), and physician demographics (position, full-time classification, physician-scientist classification, years of experience, years in the department, board certification status, gender, race/ethnicity, site of practice, academic rank, tenure track, degrees, and total salary). Total salary was defined as base compensation plus incentive bonus during the most recent fiscal year. Multivariable logistic regression models were used to identify factors associated with associate or full professor rank. A full model was first fitted with main effects, as well as all the first-order pairwise interaction terms related to gender and race, respectively. Backward stepwise elimination of non-significant (threshold: $P < 0.05$) variables was performed to reach a final model. Salary was compared by gender and race/ethnicity overall and stratified by rank. Results: The survey included data on 858 academic radiation oncologists (ROs) from 59 departments in the US. A third (33.2%) were female; 60.5% were white, 26.9% Asian and 12.7% under-represented minority (URM; by 2020 Census categories). There were 44.0% assistant professors, 32.0% associate professors, and 22.8% full professors. Multivariable logistic regression analysis showed that ROs practicing in the Midwest (OR 0.20 vs West; $P < 0.01$) or Northeast (OR 0.43 vs West; $P = 0.02$) or at an institution with 50+ faculty members (OR 1.84; $P < 0.01$) were less likely to be associate or full professors. ROs practicing at the main campus (OR 2.10; $P < 0.01$), with more years of experience (OR 0.44 0-4 vs 5-9 years; $P < 0.01$ and OR 6.41 20+ vs 5-9 years; $P < 0.01$), and with more years in the department (OR 0.10 0-4 vs 5-9 years; $P < 0.01$ and OR 3.53 20+ vs 5-9 years; $P < 0.01$) were more likely to be associate or full professors. Sex and race were not associated with associate or full professor rank. Overall, there were no significant differences in total salary between male and female instructors, assistant professors, and associate professors. However, male full professors had significantly higher mean salaries as compared to female full professors (10.4% higher; $P < 0.05$). There were no significant differences in total salary between white, Asian and URM instructors, assistant professors, or associate professors. However, white full professors had significantly higher mean salaries as compared to Asian (10.7% higher) and URM (11.8% higher) full professors ($P < 0.05$). Conclusion: We found no differences in holding senior academic ranks in radiation oncology by gender or race but did find salary gaps by gender and race at the full professor level. Future work should continue to ensure equitable compensation.

Radiation Oncology

Sarria GR, Timmerman R, Hermansen M, Malhotra SH, Chang B, Carter RD, Martinez DA, Garcia B, Sarria GJ, Giordano FA, **Chetty IJ**, Roa DE, and Li B. Longitudinal Remote SBRT/SRS Training in Latin America: A Prospective Cohort Study. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e192-e193.

Purpose/Objective(s): Opportunities for long-term clinical training in stereotactic technology are scarcely available or accessible. We report the results of upscaling a longitudinal telehealth training course on stereotactic body radiation therapy (SBRT) and stereotactic radiosurgery (SRS) for clinicians in Latin America, after successfully developing a pilot course. Materials/Methods: A longitudinal training program on implementing SBRT and SRS was provided to several radiation oncology centers in Peru and Colombia at no cost. The program consisted of regular 1-hour live video conferencing sessions weekly for 4 months with interactive didactics and a cloud-based platform for case-based learning. Participant-reported changes in confidence levels were measured in 16 practical domains of SBRT/SRS, based on 1-to-5 Likert scale levels. Pre- and post-curriculum practical knowledge-based exams were required for participation credit. Participant baseline features, completed pre- and post-curriculum surveys, overall and single professional-group confidence changes, and exam results are analyzed and reported. Results: One hundred and seventy-five different radiotherapy professionals participated. An average of 56 (SD ± 18) attendees per session were registered. Fifty (29.7%) participants completed the pre- and post-curriculum surveys, of which 30% were radiation oncologists (RO), 26% radiation therapists (RTT), 20% residents, 18% medical physicists and 6% neurosurgeons. Significant improvements were found across all 16 domains with overall mean +0.55 (SD ± 0.17, $P < 0.001$) Likert-scale points. Significant improvements in individual competences were most common among medical physicists, RTT and residents. Pre- and post-curriculum exams yielded a mean 16.15/30 (53.8 ± 20.3%) and 23.6/30 (78.7 ± 19.3%) correct answers ($P < 0.001$). Conclusion: Longitudinal telehealth training is an effective method for improving confidence and knowledge on SBRT/SRS amongst radiotherapy professionals. Remote continuing medical education should be widely adopted in lower-middle income countries.

Radiation Oncology

Schaff EM, **Bagher-Ebadian H**, **Siddiqui F**, **Zhu S**, **Sun Z**, **Ghanem AI**, **Lu M**, **Movsas B**, and **Chetty IJ**. Radiomic Analysis of Primary GTV and CTV for Prediction of Extranodal Extension Using Diagnostic CT Images in Patients With Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e104.

Purpose/Objective(s): Prediction of extranodal extension (ENE) status of the involved lymph nodes has been shown to be an important factor in the prognosis and treatment of patients with Oropharyngeal Squamous Cell Carcinomas (OPSCC). Official diagnosis of ENE occurs pathologically at the time of surgery, and typically necessitates aggressive adjuvant treatment with radiation and concurrent chemotherapy. Due to higher toxicity with trimodality therapy, definitive chemoradiation can be a preferred treatment option up front instead of surgery if there is high clinical suspicion of ENE. This study investigates the potential value of radiomic features extracted from pre-treatment primary gross tumor volume (GTV) and clinical target volume (CTV) on diagnostic contrast enhanced Computed Tomography (CE-CT) images for prediction of ENE in patients with OPSCC. Materials/Methods: For this study we identified 26 patients with pathologically confirmed OPSCC who went on to receive surgery and neck nodal dissection. Out of this group 13 were p16 positive, 13 were p16 negative, 7 were pathologic ENE positive, and 19 pathologic ENE negative. We contoured the primary tumor GTV on their pre-surgery CE-CT and added a 1 cm to create the CTV for radiomic analysis. For each patient, two sets of IBSI (Image Biomarker Standardization Initiative) validated radiomic features (N = 192 features from 11 different feature categories) were extracted from primary GTV and CTV on the diagnostic CE-CT images. Levene and Kolmogorov-Smirnov's (KS, $P < 0.05$) tests with confidence level of 95% along with absolute biserial correlation (|BSC|) with a threshold of > 0.2 were used to statistically reveal significant associations between ENE status and radiomics features. The Belsley collinearity diagnostics test was applied on the discriminant radiomic features for removing highly correlated features. Eight different Generalized-Linear Models (GLMs) were trained and tested using each individual feature along with two combined feature sets (combined discriminant features extracted from GTV and CTV). Balanced Accuracy Score (BAS), Positive predictive and negative predictive values (PPV and NPV, respectively) were used to evaluate the performance of the classifiers. Results: Four GTV-based radiomic features and two CTV-based radiomic features (both from textural feature categories) were found to be statistically significant discriminators between the two ENE cohorts. Performances for prediction of the ENE for the two classifiers trained with the combined feature sets were: GTV-based GLM: BAS/PPV/NPV = 0.765/0.724/0.805 and CTV-based GLM: 0.875/0.928/0.822. Results imply that the CTV-based features have greater predictive value compared to GTV-based features for characterization of ENE. Conclusion: This pilot study, albeit subject to confirmation in a larger patient population, suggests potential for the use of radiomics-based signatures extracted from the primary tumor for prediction of ENE in patients with OPSCC.

Radiation Oncology

Schaff EM, **Kirsch C**, **Gartrelle KJ**, **Li P**, **Khan G**, **Shah R**, **Movsas B**, **Parikh PJ**, **Siddiqui F**, and **Kwon D**. Magnetic Resonance Guided Stereotactic Ablative Radiation Therapy vs. Chemoradiation for Borderline and Locally Advanced Pancreatic Cancer: Single Institution Overall Survival Comparison. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e74-e75.

Purpose/Objective(s): Several academic institutions have investigated stereotactic MR guided adaptive radiation therapy (SMART) to safely dose escalate for locally advanced and borderline resectable pancreatic cancer with initial favorable toxicity and survival outcomes. In 2018 our institution began to evaluate SMART on trial in borderline and locally advanced patients. We previously presented toxicity outcomes for standard fractionated chemoradiation (chemoRT) and SMART groups with acute grade 3+ GI toxicity in 28% vs 11% ($P = 0.18$) and late toxicity 43% vs 36% ($P = 0.77$). The purpose of this abstract was to compare overall survival (OS) between chemoRT and SMART. Materials/Methods: In this IRB approved analysis, we retrospectively reviewed 115 consecutive patients from 2017-2020 with locally advanced or borderline resectable pancreatic cancer who were treated with neoadjuvant radiation therapy. Initially all patients received chemoRT to a dose of 50.4 Gy in 28 fractions. In September 2018 we began to investigate SMART (50Gy in 5 fractions) for these patients. OS was evaluated by Kaplan-Meier and log-rank test. Univariate and multivariate analysis was also performed on multiple treatment variables. Results: Of the patients included, 30 received chemoRT and 85 received SMART. Median

follow up for the chemoRT group was 32.8 months and for SMART was 14.9 months from last day of RT. Groups did not have significant differences in age, gender, tumor location, or initial CA 19-9. Pancreatectomy was performed in 13.3% vs 18.8% of patients in chemoRT and SMART groups. Per NCCN.1.2021 staging in the chemoRT group 33.3% were borderline (BL), 50% were locally advanced (LA), and 16.7% medically unresectable (MU) as compared to 24.7% BL, 49.4% LA, and 25.9% MU in the SMART group. Mean months of neoadjuvant chemo was slightly higher in the SMART group at 3.6 vs 2.3 months. Patients in the chemoRT arm were 36.7% African American vs 15.3% in the SMART group. When evaluated using Kaplan-Meier and log-rank test there was no difference in OS between groups (P = 0.95). Median OS from last day of RT in chemoRT and SMART groups was 10.7 vs 12.1 months. On univariate and multivariate analyses pancreatectomy was associated with improved OS, and both N2 disease at diagnosis and poor performance status (ECOG 2+) were associated with worse OS. Conclusion: Dose escalated SMART for locally advanced, borderline, and medically inoperable pancreatic cancer shows similar OS to standard fractionated chemoRT at a median 14.9 month follow up in our single institution analysis. With similar toxicity and OS between treatment modalities, SMART may be preferred due to the single week treatment course in a disease with overall very poor prognosis.

Radiation Oncology

Zhu S, **Elshaikh MA**, **Movsas B**, and **Wen N**. Automatic Prediction of 3D Radiation Dose Distribution in Prostate Cancer Treated with Volumetric Modulated Arc Therapy (VMAT) Using a Conditional Generative Adversarial Network (cGAN). *Int J Radiat Oncol Biol Phys* 2021; 111(3):e147.

Purpose/Objective(s): VMAT is a commonly used technique for the treatment of prostate cancer, but the planning process can be time-consuming due to the inherent complexity of the iterative optimizations. In this study, we aim to show the efficacy of a conditional generative adversarial network (cGAN) in automatically predicting the 3D radiation dose distribution trained with previously delivered plans. Materials/Methods: In an IRB-approved analysis, we obtained the data of 167 patients with prostate adenocarcinoma who received definitive RT at our institution. All included cases were planned with VMAT technique with a prescribed dose of 78 Gy in 39 fx or 79.2 Gy in 44 fx to the prostate gland +/- seminal vesicles. For each patient, the inputs to the model were 6 structure masks (PTV and 5 OARs including bladder, rectum, penile bulb, and femoral heads), all resampled to voxel size of 2.5mm x 2.5mm x 3.0mm to be consistent with the grid size for dose, and the model predicts a 3D radiation dose distribution. The cGAN's generator was a modified 3D U-net, and its discriminator was a 5-layer 3D convolutional neural network. For training, mean absolute error (MAE) and binary cross entropy were used as the loss functions for the generator and discriminator, respectively, with Adam as the optimizers. Forty cases were randomly selected for testing only, and the remaining 127 formed the training set. The algorithm was implemented in Python 3.8 with PyTorch 1.7 as the framework. Model training was performed on NVIDIA Tesla V100 GPU. Model performance was assessed by comparing dosimetric metrics (based on institutional and RTOG 0415 guidelines) between the predicted doses (normalized to PTV maximal dose of 107%) and clinical doses with two-tailed paired t-test. Results: The model was trained for 300 epochs. On the independent test set, the mean MAE for the predicted 3D dose distribution was 1.6 Gy per voxel (range, 0.9 – 4.5 Gy). Dosimetric comparison (Table 1) demonstrated that the predicted doses had similar to improved PTV coverage and comparable dose to OARs, except for the femoral heads for which the model predicted higher D5's that still fell within dose constraint of < 50 Gy. Conclusion: We demonstrated that, with the structures of the PTV and OARs as inputs, the 3D cGAN is excellent at the rapid prediction of radiation dose distributions of VMAT plans for prostate cancer that closely resemble clinically delivered doses. With further work on the deliverability of the predicted doses, our method can significantly increase the efficiency of treatment planning.

Surgery

Chuong MD, **Kirsch C**, Herrera R, Rubens M, Gungor G, **Schaff EM**, **Dolan J**, **Kim J**, Mittauer KE, Kotecha R, Gutierrez A, **Doemer AJ**, Ugurluer G, **Kwon D**, **Khan G**, Alvarez D, Ucar A, Asbun H, Ozyar E, and **Parikh PJ**. Long-Term Multi-Institutional Outcomes of 5-Fraction Ablative Stereotactic MR-Guided Adaptive Radiation Therapy (SMART) for Inoperable Pancreas Cancer With Median Prescribed Biologically Effective Dose of 100 Gy10. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S147-S148.

Purpose/Objective(s): Randomized trials have shown improved local control (LC) but no overall survival (OS) benefit with the addition of non-ablative radiation therapy (RT) dose compared to chemotherapy (CT) alone for pancreas cancer (PCa). Emerging data suggest that dose-escalated RT may improve LC and OS. A few studies suggest that stereotactic magnetic resonance-guided adaptive RT (SMART) can facilitate the safe delivery of ablative dose for inoperable PCa, although long-term outcomes are not well understood. Materials/Methods: Inoperable PCa patients who received SMART were identified from the RSSearch Registry. Patients with < 3 months (mo.) follow-up after SMART were excluded. LC, progression free survival (PFS), and OS were estimated using the Kaplan-Meier method. LC was evaluated according to RECIST 1.1 criteria. Acute toxicity was considered within 90 days of SMART and evaluated by CTCAE v4 criteria. Results: A total of 148 PCa patients were treated on a 0.35T MR LINAC across 3 institutions between 2018-2020. Median age was 68 years (range 47-91), and 73.6% had ECOG 0-1 performance status. Patients had locally advanced (57.4%), borderline resectable (29.1%), or medically inoperable (13.5%) disease. Median CA19-9 at diagnosis was 202.1 U/mL (range 0.9-21,281). Induction CT was delivered to 89.2% for a median 3.9 mo (range 0.2-11.3); FOLFIRINOX (52.7%) or gemcitabine/nab-paclitaxel (23.4%) were common. Median prescribed RT dose was 50 Gy (range 40-50) in 5 fractions, mostly in consecutive days (96.6%) and in breath hold (95.3%). Median biologically effective dose (BED10) was 100 Gy10. All patients were treated with real-time tissue tracking and automated beam gating without fiducial markers. An elective target volume was rarely used (25%). Pancreaticoduodenectomy was performed in 23% at a median 46 days (range 34-304) after SMART. Median follow-up was 16 mo. from diagnosis for all patients (range, 4-39). Median, 1-year, and 2-year LC was not reached (NR), 94.6%, and 83%, respectively. Median, 1-year, and 2-year PFS was 18 mo., 72%, and 35.9%, respectively. Median, 1-year, and 2-year OS was 26 mo., 82%, and 52.7%, respectively. Acute and late grade 3 toxicity possibly related to SMART occurred in 4.1% and 12.8%, respectively. There was no reported grade 4+ toxicity. Conclusion: To our knowledge, this is the largest reported analysis of 5-fraction SMART for inoperable PCa. These data add to the evidence that ablative radiation dose may improve long-term outcomes including OS. Prospective evaluation of this novel approach is warranted with attention directed at optimizing patient selection, understanding the clinical significance of cumulative dose delivered across all adapted fractions, and assessing treatment response after the delivery of ablative dose.

Surgery

Mohamed A, **Kitajima T**, **Shamaa T**, **Elsabbagh AM**, **Yoshida A**, **Abouljoud MS**, and **Nagai S**. The Impact of Thromboelastography on Decreasing Blood Product Usage in Liver Transplantation. *J Am Coll Surg* 2021; 233(5):e201.

Introduction: Thromboelastography (TEG) has emerged as a tool to guide resuscitation in Liver Transplantation (LT). We aim to identify effects of TEG utilization on product use and blood loss in LT. Methods: Adult patients (age >18-years-old) who received LT between 2014 and 2020 were retrospectively reviewed. Living donor, simultaneous/multi-organ transplants, re-transplants, and pediatric transplants were excluded. Impact of TEG on blood products and intraoperative blood loss was analyzed. A subgroup analysis was done based on INR. The median, 75th and 90th percentile of INR at transplant were used as cut-off values. Patients were classified into four categories: no, mild, moderate, and severe coagulopathy groups. Results: Four-hundred-fifty-one patients met inclusion criteria and were separated into TEG(n=144) vs non-TEG(n=307). Background characteristics between these groups were comparable. Median blood products used were similar between TEG and non-TEG groups. In the subgroup analysis, there was a significant decrease in product use in the TEG-group with moderate coagulopathy, compared to the non-TEG group: pRBC (4.5vs7.0 units, p=0.002); FFP (6.0vs9.0 units, p=0.005); Cryoprecipitate (1.0vs2.0 units, p=0.005). Tranexamic acid (TXA) use was significantly higher in the TEG-group with median values of 1000vs0 mg (p<0.001). There was no difference in median blood loss. In the no, mild, and severe coagulopathy groups, there was no difference in blood product use, blood loss, or TXA use between groups. Conclusion: TEG guided resuscitation in LT resulted in a decrease in product usage, and more utilization of TXA in patients with moderate coagulopathy defined as INR between 2.2 and 2.8.

Surgery

Qureshi SA, **Prasad M Nalamati S**, **Reickert CA**, and **Itenberg ER**. Bleeding Complications after Rubber Band Ligation of Internal Hemorrhoids in Anticoagulated Patients. *J Am Coll Surg* 2021; 233(5):S52.

Introduction: Symptomatic internal hemorrhoids are a common colorectal disease that is often treated in clinic by rubber band ligation (RBL), with a bleeding complication rate around 1.8% of patients. There are sparse data evaluating hemorrhage after rubber band ligation in anticoagulated patients, except for a few case reports and series stating it is not recommended. Methods: A retrospective review was conducted of all patients who underwent rubber band ligation in the office of the colorectal surgery department for internal hemorrhoids while on anticoagulation, from January 1, 2010 to August 30, 2020. The patients were evaluated for any postoperative issue within 30 days. A bleeding event was considered significant if the patient required hospital admission, blood transfusion, or additional procedures to stop bleeding. Results: Sixteen patients were identified on anticoagulation (31% [n=5] apixaban, 50% [n=8] warfarin, 19% [n=3] Xarelto); they had 30 clinic visits with a total of 33 band ligations. The mean age of patients was 74.5 years (range 60-92 years), 62.5% were male (n=10), with a mean BMI of 32.4±6.6 kg/m2. There were 2 significant bleeding events (6.67%) while on warfarin and apixaban; both of these patients were admitted to the hospital (3 and 13 days post-procedure), and 1 received 2 blood transfusions. No patient required any surgical or endoscopic intervention. Conclusion: While the risk of bleeding after RBL for hemorrhoids is slightly higher in fully anticoagulated patients, it was well tolerated by the majority. Our results support that RBL may be done in this high-risk population with close monitoring.

Surgery

Schaff EM, **Kirsch C**, **Gartrelle KJ**, **Li P**, **Khan G**, **Shah R**, **Movsas B**, **Parikh PJ**, **Siddiqui F**, and **Kwon D**. Magnetic Resonance Guided Stereotactic Ablative Radiation Therapy vs. Chemoradiation for Borderline and Locally Advanced Pancreatic Cancer: Single Institution Overall Survival Comparison. *Int J Radiat Oncol Biol Phys* 2021; 111(3):e74-e75.

E.M. Schaff, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Several academic institutions have investigated stereotactic MR guided adaptive radiation therapy (SMART) to safely dose escalate for locally advanced and borderline resectable pancreatic cancer with initial favorable toxicity and survival outcomes. In 2018 our institution began to evaluate SMART on trial in borderline and locally advanced patients. We previously presented toxicity outcomes for standard fractionated chemoradiation (chemoRT) and SMART groups with acute grade 3+ GI toxicity in 28% vs 11% (P = 0.18) and late toxicity 43% vs 36% (P = 0.77). The purpose of this abstract was to compare overall survival (OS) between chemoRT and SMART. Materials/Methods: In this IRB approved analysis, we retrospectively reviewed 115 consecutive patients from 2017-2020 with locally advanced or borderline resectable pancreatic cancer who were treated with neoadjuvant radiation therapy. Initially all patients received chemoRT to a dose of 50.4 Gy in 28 fractions. In September 2018 we began to investigate SMART (50Gy in 5 fractions) for these patients. OS was evaluated by Kaplan-Meier and log-rank test. Univariate and multivariate analysis was also performed on multiple treatment variables. Results: Of the patients included, 30 received chemoRT and 85 received SMART. Median follow up for the chemoRT group was 32.8 months and for SMART was 14.9 months from last day of RT. Groups did not have significant differences in age, gender, tumor location, or initial CA 19-9. Pancreatectomy was performed in 13.3% vs 18.8% of patients in chemoRT and SMART groups. Per NCCN.1.2021 staging in the chemoRT group 33.3% were borderline (BL), 50% were locally advanced (LA), and 16.7% medically unresectable (MU) as compared to 24.7% BL, 49.4% LA, and 25.9% MU in the SMART group. Mean months of neoadjuvant chemo was slightly higher in the SMART group at 3.6 vs 2.3 months. Patients in the chemoRT arm were 36.7% African American vs 15.3% in the SMART group. When evaluated using Kaplan-Meier and log-rank test there was no difference in OS between groups (P = 0.95). Median OS from last day of RT in chemoRT and SMART groups was 10.7 vs 12.1 months. On univariate and multivariate analyses pancreatectomy was associated with improved OS, and both N2 disease at diagnosis and poor performance status (ECOG 2+) were associated with worse OS. Conclusion: Dose escalated SMART for locally advanced, borderline, and medically inoperable pancreatic cancer shows similar OS to standard fractionated chemoRT at a median 14.9 month follow up

in our single institution analysis. With similar toxicity and OS between treatment modalities, SMART may be preferred due to the single week treatment course in a disease with overall very poor prognosis.

Surgery

Shamaa MT, **Kitajima T**, **Ivanics T**, **Shimada S**, **Mohamed A**, **Rizzari MD**, **Collins KM**, **Yoshida A**, **Abouljoud MS**, and **Nagai S**. Effect of Season and Climate Regions on Liver Transplant Waitlist Outcomes. *J Am Coll Surg* 2021; 233(5):S271.

Introduction: We previously reported that post-liver transplantation (LT) outcomes are worse in colder regions, possibly due to the effect of cold weather. The effect of cold climate on waitlist outcomes remains unknown. The aim of this study was to investigate the waitlist outcomes of LT candidates listed in cold states compared with warm states. Methods: We analyzed the data from United Network for Organ Sharing registry for 98,965 adult patients (18 years or older) who were listed for single-organ, deceased LT between 2010 and 2019. Two seasons were defined: warm (April to October; n = 58,769) and cold (November to March; n = 40,196). States were categorized based on their mean winter temperature: cold states (0°F to 40°F) and warm states (40°F to 70°F). Waitlist outcomes at 90 days and 1 year were compared according to the season and states using the Fine-Gray hazard regression model. Results: LT candidates listed in cold states were younger (median age 40 vs 43 years; $p < 0.001$), with lower median Model for End-Stage Liver Disease score (16 vs 17; $p < 0.001$), and were less likely to be on dialysis (7.6% vs 5.2%; $p < 0.001$) or require life support (3.7% vs 5.2%; $p < 0.001$) compared with warm states. In comparison with LT candidates listed in warm states, LT candidates listed in cold states had a significantly higher risk of waitlist mortality, lower chance of transplant probability, and recovery at 90 days and 1 year, even after adjusting for the season and patient characteristics at listing. Conclusion: LT candidates had worse short-term and long-term waitlist outcomes when listed in cold states compared with warm states.

Surgery

Stefanou A, **Gardner CW**, and **Rubinfeld IS**. Comparison of Common Minimally Invasive Operations Using Patient Safety Indicators (PSI). *J Am Coll Surg* 2021; 233(5):e98.

Introduction: The PSI 90, is used to monitor hospital safety, quality, and value. It is composed predominantly of PSI 9 (perioperative hemorrhage), 11 (postoperative respiratory failure), 12 (perioperative deep vein thrombosis/pulmonary embolus), and 13 (postoperative sepsis). MIS has been shown to have fewer complications. We aim to evaluate the rates of PSI between MIS in common procedures. Methods: Using a health system database we examined cases that underwent MIS or open appendectomy, cholecystectomy, colectomy, and hysterectomy, and compared them across the four main PSIs over a 2-year period. Operations were compared based on comorbidities, admitting service and procedure. Outcome of interest was surgical approach. Univariate and multivariate analysis was performed in R. Results: Our sample included a total of 1800 MIS and 1580 open operations. Rates of PSI were: PSI 9, 1.8%, PSI 11, 2.7%, PSI 12, 4.2%, and PSI 13, 5.6%. Patients were similar in comorbidities and demographics, with the exception of open procedures being more likely in cancer patients. Univariate analysis found no significant differences across surgical groupings of open vs MIS, or PSI type. Multivariate regression analysis did not show any significant association in MSI operative status and PSI incidence. Conclusion: While minimally invasive surgery has known clinical benefits, this has not translated into a clear improvement across the AHRQ PSI. Additionally, there are still other modifiable factors that would allow for improvement of PSI 90 in minimally invasive surgery.

Urology

Dai Z, Jambor I, Taimen P, **Pantelic M**, **Elshaikh MA**, **Dabaja A**, **Rogers C**, Ettala O, Boström P, Aronen H, Merisaari H, and **Wen N**. Accurate Prostate Cancer Detection and Segmentation Using Non-Local Mask R-CNN With Histopathological Ground Truth. *Int J Radiat Oncol Biol Phys* 2021; 111(3):S45.

Z. Dai, Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, United States

Purpose/Objective(s): We aim to develop deep learning (DL) models to accurately detect and segment intraprostatic lesions (IL) on biparametric MRI (bp-MRI). Materials/Methods: Three patient cohorts with

ground truth IL delineated on different modalities were collected. 158 patients from two datasets had suspicious ILs delineated based on bp-MRI: 97 patients were from PROSTATEx-2 Challenge with biopsy result independent from bp-MRI based delineation, 61 patients were from IMPROD clinical Trial with biopsy done for each delineation; 64 patients from IMPROD clinical Trial had ILs identified and delineated by using whole mount prostatectomy specimen sections as reference standard; 40 private patients were unlabeled. We proposed a non-local Mask R-CNN to improve segmentation accuracy by addressing the imperfect registration issue between MRI modalities. We also proposed to post aggregate 2D predictions to estimate IL volumes within the whole prostatic gland and keep top-5 3D predictions for each patient. In order to explore the small dataset problem, we employed different learning techniques including transfer learning and semi-supervised learning with pseudo labelling. We experimented with two label selection strategies to see how they affected model performance. The first strategy kept only one prediction by referring to biopsy result, in order to minimize false positives; while the second strategy kept all top-5 predictions. 3D top-5 detection rate, dice similarity coefficient (DSC), 95 percentile Hausdorff Distance (95 HD, mm) and true positive ratio (TPR) were our evaluation metrics. We compared DL model prediction with prostatectomy-based ground truth delineation to accurately evaluate the boundary and malignancy level. We separately evaluated ILs of all Gleason Grade Group (GGG) and clinically significant ILs (GGG > 2). Results: Main results are summarized in Table 1. Conclusion: Our proposed method demonstrates state-of-art performance in the detection and segmentation of ILs and shows great effectiveness for clinically significant ILs.

Urology

Qureshi SA, **Prasad M Nalamati S**, **Reickert CA**, and **Itenberg ER**. Bleeding Complications after Rubber Band Ligation of Internal Hemorrhoids in Anticoagulated Patients. *J Am Coll Surg* 2021; 233(5):S52.

Introduction: Symptomatic internal hemorrhoids are a common colorectal disease that is often treated in clinic by rubber band ligation (RBL), with a bleeding complication rate around 1.8% of patients. There are sparse data evaluating hemorrhage after rubber band ligation in anticoagulated patients, except for a few case reports and series stating it is not recommended. Methods: A retrospective review was conducted of all patients who underwent rubber band ligation in the office of the colorectal surgery department for internal hemorrhoids while on anticoagulation, from January 1, 2010 to August 30, 2020. The patients were evaluated for any postoperative issue within 30 days. A bleeding event was considered significant if the patient required hospital admission, blood transfusion, or additional procedures to stop bleeding. Results: Sixteen patients were identified on anticoagulation (31% [n=5] apixaban, 50% [n=8] warfarin, 19% [n=3] Xarelto); they had 30 clinic visits with a total of 33 band ligations. The mean age of patients was 74.5 years (range 60-92 years), 62.5% were male (n=10), with a mean BMI of 32.4±6.6 kg/m2. There were 2 significant bleeding events (6.67%) while on warfarin and apixaban; both of these patients were admitted to the hospital (3 and 13 days post-procedure), and 1 received 2 blood transfusions. No patient required any surgical or endoscopic intervention. Conclusion: While the risk of bleeding after RBL for hemorrhoids is slightly higher in fully anticoagulated patients, it was well tolerated by the majority. Our results support that RBL may be done in this high-risk population with close monitoring.

HFHS Publications on COVID-19

Anesthesiology
Fayed M, **Patel N**, **Yeldo N**, **Nowak K**, **Penning DH**, **Vasconcelos Torres F**, **Natour AK**, and **Chhina A**. Effect of Intubation Timing on the Outcome of Patients With Severe Respiratory Distress Secondary to COVID-19 Pneumonia. *Cureus* 2021; 13(11). PMID: 34804753. Full Text

Diagnostic Radiology
Mousavi Mojab SZ, **Shams S**, Fotouhi F, and **Soltanian-Zadeh H**. EpistoNet: an ensemble of Epistocracy-optimized mixture of experts for detecting COVID-19 on chest X-ray images. *Sci Rep* 2021; 11(1):21564. PMID: 34732741. Full Text

Emergency Medicine
Liangou A, Tasoglou A, Huber HJ, Wistrom C, **Brody K**, Menon PG, **Bebekoski T**, **Menschel K**, **Davidson-Fiedler M**, DeMarco K, Salphale H, Wistrom J, Wistrom S, and Lee RJ. A method for the identification of COVID-19 biomarkers in human breath using Proton Transfer Reaction Time-of-Flight Mass Spectrometry. *EClinicalMedicine* 2021; 42:101207. PMID: 34841237. Full Text

Hematology-Oncology
Hoogenboom WS, Alamuri TT, McMahon DM, **Balanchivadze N**, **Dabak V**, Mitchell WB, Morrone KB, Manwani D, and Duong TQ. Clinical outcomes of COVID-19 in patients with sickle cell disease and sickle cell trait: A critical appraisal of the literature. *Blood Rev* 2021; Epub ahead of print.:100911. PMID: 34838342. Full Text

Hematology-Oncology
Schmidt AL, Tucker MD, Bakouny Z, Labaki C, Hsu CY, Shyr Y, Armstrong AJ, Beer TM, Bijjula RR, Bilen MA, Connell CF, Dawsey SJ, Faller B, Gao X, Gartrell BA, Gill D, Gulati S, Halabi S, **Hwang C**, Joshi M, Khaki AR, Menon H, Morris MJ, Puc M, Russell KB, Shah NJ, Sharifi N, Shaya J, Schweizer MT, Steinharter J, Wulff-Burchfield EM, Xu W, Zhu J, Mishra S, Grivas P, Rini BI, Warner JL, Zhang T, Choueiri TK, Gupta S, and McKay RR. Association Between Androgen Deprivation Therapy and Mortality Among Patients With Prostate Cancer and COVID-19. *JAMA Netw Open* 2021; 4(11). PMID: 34767021. Full Text

Hospital Medicine
Li P, Zhao W, **Kaatz S**, **Latack K**, **Schultz L**, and **Poisson L**. Factors Associated With Risk of Postdischarge Thrombosis in Patients With COVID-19. *JAMA Netw Open* 2021; 4(11). PMID: 34807256. Full Text

Infectious Diseases
Axfors C, Janiaud P, **Cao DH**, **Hines J**, **Jennings JH**, **Kotecha A**, **Murphy E**, **Ramesh M**, **Sharma G**, **Tang A**, **Tatem G**, et al. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis* 2021; 21(1):1170. PMID: 34800996. Full Text

Nephrology
Axfors C, Janiaud P, **Cao DH**, **Hines J**, **Jennings JH**, **Kotecha A**, **Murphy E**, **Ramesh M**, **Sharma G**, **Tang A**, **Tatem G**, et al. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis* 2021; 21(1):1170. PMID: 34800996. Full Text

Neurology
Zaidi SK, Ahmed F, Alkhatabi H, **Hoda MN**, and Al-Qahtani M. Nebulization of low-dose s-nitrosoglutathione in diabetic stroke enhances benefits of reperfusion and prevents post-thrombolysis hemorrhage. *Biomolecules* 2021; 11(11). PMID: Not assigned. Full Text

Pathology and Laboratory Medicine
Axfors C, Janiaud P, **Cao DH**, **Hines J**, **Jennings JH**, **Kotecha A**, **Murphy E**, **Ramesh M**, **Sharma G**, **Tang A**, **Tatem G**, et al. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis* 2021; 21(1):1170. PMID: 34800996. Full Text

Public Health Sciences
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Pulmonary and Critical Care Medicine
Axfors C, Janiaud P, **Cao DH**, **Hines J**, **Jennings JH**, **Kotecha A**, **Murphy E**, **Ramesh M**, **Sharma G**, **Tang A**, **Tatem G**, et al. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis* 2021; 21(1):1170. PMID: 34800996. Full Text

Sleep Medicine
Cheng P, Casement MD, Cuellar R, Johnson DA, **Kalmbach D**, **Cuamatzi Castelan A**, and **Drake CL**. Sleepless in COVID-19: racial disparities during the pandemic as a consequence of structural inequity. *Sleep* 2021; Epub ahead of print. PMID: 34788453. Full Text

Surgery
Fayed M, **Patel N**, **Yeldo N**, **Nowak K**, **Penning DH**, **Vasconcelos Torres F**, **Natour AK**, and **Chhina A**. Effect of Intubation Timing on the Outcome of Patients With Severe Respiratory Distress Secondary to COVID-19 Pneumonia. *Cureus* 2021; 13(11). PMID: 34804753. Full Text