

Henry Ford Health System Publication List – October 2020

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 **145 unique citations** listed this month, with **9 articles** and **2 conference abstracts 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

Anesthesiology

Frisoli TM, So CY, Guruswamy JG, Chebl AB, Lee JC, and Eng MH. Vacuuming in Crowded Dangerous Spaces: Aspiration of Large Ascending Aortic Thrombus. *JACC: Case Reports* 2020; 2(12):1979-1983. PMID: Not assigned. [Full Text](#)

T.M. Frisoli, Center for Structural Heart Disease, Henry Ford Hospital, 2799 West Grand Boulevard, CFP Fourth Floor, Detroit, MI, United States

A patient had a stroke caused by a large, pedunculated aortic ascending mass and was deemed at high risk for near-term recurrent stroke. This case illustrates percutaneous aspiration thrombectomy of ascending aortic thrombus with the AngioVac system (Angiodynamics, Latham, New York), with conscious sedation for early stroke detection and with endovascular cerebral embolic protection. (Level of Difficulty: Intermediate.)

Anesthesiology

Nemeh H, Coba V, Chulkov M, Gupta A, Yeldo N, Chamogeorgakis T, Tanaka D, Allenspach L, Simanovski J, and Shanti C. Lung Transplantation for the Treatment of Vaping Induced, Irreversible, End Stage Lung Injury. *Ann Thorac Surg* 2020; Epub ahead of print. PMID: 33130115. [Full Text](#)

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Recently, there has been a rise in the incidence of E-cigarettes/Vaping Associated Lung Injury (EVALI) in the United States mostly involving Tetrahydrocannabinol (THC)(1). Present treatment strategies for

EVALI are aimed at controlling the inflammatory and infectious etiologies in addition to supportive care(2). While most patients improve with supportive measures(3,4) the long-term pulmonary effects of this illness are still not well defined. In this report, we describe a case of EVALI resulting in progressive, irreversible destruction of the lung parenchyma that was treated with double lung transplantation.

Behavioral Health Sciences/Psychiatry

Katato H, Smith D, and Akinyemi E. Residency Training in a Healthcare Crisis. *Acad Psychiatry* 2020; Epub ahead of print. PMID: 33058048. [Full Text](#)

Henry Ford Hospital/Wayne State University, Detroit, MI, USA.

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Behavioral Health Sciences/Psychiatry

Mun M, Gautam M, Maan R, and Krayem B. An Increased Presence of Male Personalities in Dissociative Identity Disorder after Initiating Testosterone Therapy. *Case Rep Psychiatry* 2020; 2020. PMID: 33083080. [Full Text](#)

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Patients with gender dysphoria (GD) report significant dissociative symptoms and are found to have a high prevalence of a dissociative disorder of any kind. When GD patients elect to undergo cross-sex hormone therapy, there is a significant reduction in dissociative symptoms. However, to the best of our knowledge, there are no known case reports that describe an alteration of personalities in dissociative identity disorder after initiating cross-sex hormone therapy. Thus, we present a case of a 20-year-old transgender male with GD, whom after initiating cross-sex hormone therapy with testosterone experienced an increased presence of his existing male personalities.

Cardiology and Cardiovascular Research

Al-Darzi WK, Hana A, Lahiri MK, Dagher C, Greenberg JC, Alaswad K, Rabbani BT, McCord JK, and Reddy M. Diffuse B Cell Lymphoma Leading to Complete Heart Block: Is This Transient or Permanent? *Am J Case Rep* 2020; 21:e925760. PMID: 33093439. [Request Article](#)

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BACKGROUND Cardiac lymphomas can lead to heart block through tumor disruption of the cardiac conduction system. It is reported that with cardiac tumor treatment, conduction abnormalities can resolve. We present a case of cardiac lymphoma resulting in complete heart block requiring a pacemaker, followed by reduction of the pacing burden after chemotherapy. **CASE REPORT** A 72-year-old woman with a medical history of hypertension, hypothyroidism, and persistent atrial fibrillation presented with dyspnea on exertion and fatigue for 2 weeks. Electrocardiography revealed complete heart block with junctional bradycardia of 48 beats per min. Transthoracic echocardiography demonstrated preserved left ventricular systolic function along with a large mass (3.6×3.7 cm). An endomyocardial biopsy was consistent with diffuse large B cell lymphoma, and the cardiac involvement was thought to be secondary based on positron emission tomography scan findings. Her clinical course was complicated by an episode of syncope deemed to be due to transient asystole, and an urgent single-chamber permanent pacemaker was implanted. Chemotherapy was initiated with R-CHOP, and, following the second cycle of chemotherapy, a positron emission tomography scan revealed no increased radiotracer uptake and thus resolution of all tumors. An echocardiogram 6 weeks after chemotherapy showed complete resolution of the cardiac mass. Subsequent serial pacemaker checks demonstrated improvement of atrioventricular nodal function as manifested by reduced pacing burden. **CONCLUSIONS** Lymphoma with cardiac involvement can lead to conduction abnormalities, including CHB, and heart block in the setting of these tumors may be reversible with appropriate therapy; however, implantation of a pacemaker remains inevitable in some cases.

Cardiology and Cardiovascular Research

Basir MB, Eng MH, Villablanca P, Anderson MB, Zaidan M, Wang DD, Alaswad K, O'Neill WW, and Alqarqaz M. Alternative Access for Mechanical Circulatory Support. *Structural Heart* 2020; Epub ahead of print. PMID: Not assigned. [Full Text](#)

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Technological advancements and the development of shock teams and protocols have led to increasing utilization of mechanical circulatory support (MCS) devices. These large-bore devices are used to provide hemodynamic support in patients undergoing complex cardiovascular procedures and to support end-organ perfusion in those with heart failure or cardiogenic shock. Vascular access complications are common and limit the therapeutic and hemodynamic benefits of such devices. In this review, the authors discuss common techniques used to overcome hostile femoral anatomy and review alternative accesses that can be used for the safe delivery of MCS devices.

Cardiology and Cardiovascular Research

Fleg JL, **Keteyian SJ**, Peterson PN, Benzo R, Finkelstein J, Forman DE, Gaalema DE, Cooper LS, Punturieri A, Joseph L, Shero S, and Zieman S. Increasing Use of Cardiac and Pulmonary Rehabilitation in Traditional and Community Settings: OPPORTUNITIES TO REDUCE HEALTH CARE DISPARITIES. *J Cardiopulm Rehabil Prev* 2020; Epub ahead of print. PMID: 33074849. [Full Text](#)

National Heart Lung and Blood Institute, Bethesda, Maryland (Drs Fleg, Cooper, and Punturieri and Ms Shero); Henry Ford Hospital, Detroit, Michigan (Dr Keteyian); Denver Health Medical Center, Denver, and University of Colorado Anschutz Medical Center, Aurora, Colorado (Dr Peterson); Mayo Clinic, Rochester, Minnesota (Dr Benzo); Icahn School of Medicine at Mount Sinai, New York (Dr Finkelstein); University of Pittsburgh, Pittsburgh, Pennsylvania (Dr Forman); University of Vermont, Burlington (Dr Gaalema); and National Institute on Aging, Bethesda, Maryland (Drs Joseph and Zieman).

Although both cardiac rehabilitation (CR) and pulmonary rehabilitation (PR) are recommended by clinical practice guidelines and covered by most insurers, they remain severely underutilized. To address this problem, the National Heart, Lung, and Blood Institute (NHLBI), in collaboration with the National Institute on Aging (NIA), developed Funding Opportunity Announcements (FOAs) in late 2017 to support phase II clinical trials to increase the uptake of CR and PR in traditional and community settings. The objectives of these FOAs were to (1) test strategies that will lead to increased use of CR and PR in the US population who are eligible based on clinical guidelines; (2) test strategies to reduce disparities in the use of CR and PR based on age, gender, race/ethnicity, and socioeconomic status; and (3) test whether increased use of CR and PR, whether by traditional center-based or new models, is accompanied by improvements in relevant clinical and patient-centered outcomes, including exercise capacity, cardiovascular and pulmonary risk factors, and quality of life. Five NHLBI grants and a single NIA grant were funded in the summer of 2018 for this CR/PR collaborative initiative. A brief description of the research to be developed in each grant is provided.

Cardiology and Cardiovascular Research

Fram G, Wang DD, Malette K, Villablanca P, Kang G, So K, Basir MB, Khan A, McKinnon JE, Zervos M, and O'Neill WW. Cardiac Complications Attributed to Hydroxychloroquine: A systematic review of the Literature Pre-COVID-19. *Curr Cardiol Rev* 2020; Epub ahead of print. PMID: 33059567. [Request Article](#)

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INTRODUCTION: Hydroxychloroquine has been used for rheumatological diseases for many decades and is considered a safe medication. With the COVID-19 outbreak, there has been an increase in reports associating cardiotoxicity with hydroxychloroquine. It is unclear if cardiotoxic profile of hydroxychloroquine

is previously underreported in the literature, or a new manifestation of COVID-19 and therapeutic interventions. This manuscript evaluates the incidence of cardiotoxicity associated with hydroxychloroquine prior to onset of COVID-19. METHODS: PubMed, EMBASE, and Cochrane databases were searched for keywords derived from MeSH terms, prior to 4/9/2020. Inclusion eligibility was based on appropriate reporting of cardiac conditions and study design. RESULTS: Sixty-nine articles were identified (58 case reports, 11 case series). Majority (84%) of patients were female, with a median age of 49.2 (range 16-92) years. Fifteen of 185 patients with cardiotoxic events were in the setting of acute intentional overdose. In acute overdose, the median ingestion was 17,857 \pm 14,873 mg. Two of 15 patients died after acute intoxication. In patients with long-term hydroxychloroquine use (10.5 \pm 8.9 years), new onset systolic heart failure occurred in 54 of 155 patients (35%) with median cumulative ingestion of 1,493,800 \pm 995,517 mg. The majority of patients improved with withdrawal of hydroxychloroquine and standard therapy. CONCLUSIONS: Millions of hydroxychloroquine doses are prescribed annually. Prior to COVID-19 pandemic, cardiac complications attributed to hydroxychloroquine were uncommon. Further studies are needed to understand the impact of COVID-19 on the cardiovascular system to understand presence or absence of potential medication interactions with hydroxychloroquine in this new pathophysiological state.

Cardiology and Cardiovascular Research

Frisoli TM, So CY, Guruswamy JG, Chebl AB, Lee JC, and Eng MH. Vacuuming in Crowded Dangerous Spaces: Aspiration of Large Ascending Aortic Thrombus. *JACC: Case Reports* 2020; 2(12):1979-1983. PMID: Not assigned. [Full Text](#)

T.M. Frisoli, Center for Structural Heart Disease, Henry Ford Hospital, 2799 West Grand Boulevard, CFP Fourth Floor, Detroit, MI, United States

A patient had a stroke caused by a large, pedunculated aortic ascending mass and was deemed at high risk for near-term recurrent stroke. This case illustrates percutaneous aspiration thrombectomy of ascending aortic thrombus with the AngioVac system (Angiodynamics, Latham, New York), with conscious sedation for early stroke detection and with endovascular cerebral embolic protection. (Level of Difficulty: Intermediate.)

Cardiology and Cardiovascular Research

Gorgis S, Dabbagh MF, Mishra K, Ahluwalia G, Hana A, Fram G, Dhillon D, Lemor A, Khan A, Miller D, Kaatz S, O'Neill WW, and Wang DD. Unprotected discharge: absence of stroke prevention strategies in patients with atrial fibrillation admitted for bleeding. *J Interv Card Electrophysiol* 2020; Epub ahead of print. PMID: 33119818. [Full Text](#)

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PURPOSE: Patients with atrial fibrillation or flutter (AF) on anticoagulation (AC) for stroke prevention are at an increased risk of bleeding. A common clinical dilemma is deciding when to safely restart AC following a bleed. Although studies have shown better outcomes with re-initiation of AC after hemostasis, there are clinical barriers to restarting AC. Left atrial appendage occlusion (LAAO) is a safe and efficacious alternative for patients who are unable to tolerate AC following major bleeding. We aimed to evaluate the rate of stroke prevention strategies instituted at time of discharge in patients with AF on AC who had been hospitalized for a bleeding event. **METHODS:** We retrospectively identified patients with AF on AC admitted for bleeding between January 2016 and August 2019. The type of AC, form of bleeding, and CHA(2)DS(2)VASc were collected. Stroke prevention strategies upon discharge and at 3 months were noted. **RESULTS:** One hundred seventy-four patients with AF on AC were hospitalized with a bleeding event, of which 10.9% died. Among patients who survived, AC was restarted in 45.2% of patients, 9.7% were referred for LAAO, and 45.1% were discharged without stroke prevention strategy. At 3 months, 32.6% of patients still had no documented stroke prophylaxis. Those referred for LAAO had, on

average, higher CHA(2)DS(2)VASc (5 ± 1 vs 4 ± 1 , $p = 0.007$). CONCLUSIONS: A significant number of patients with AF hospitalized for bleeding were discharged with no plan for stroke prophylaxis. Despite its safety and efficacy, LAAO appears to be an underutilized alternative in AF patients with high bleeding risk.

Cardiology and Cardiovascular Research

Lanfeer DE, Luzum JA, She R, Gui H, Donahue MP, O'Connor CM, Adams KF, Sanders-van Wijk S, Zeld N, Maeder MT, Sabbah HN, Kraus WE, Brunner-La Rocca HP, Li J, and Williams LK. Polygenic Score for Beta-Blocker Survival Benefit in European Ancestry Patients with Reduced Ejection Fraction Heart Failure. *Circ Heart Fail* 2020; Epub ahead of print. PMID: 33012170. [Full Text](#)

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Background: Beta-blockers (BB) are mainstay therapy for heart failure with reduced ejection fraction (HFrEF). However, individual patient responses to BB vary, which may be partially due to genetic variation. The goal of this study was to derive and validate the first polygenic response predictor (PRP) for BB survival benefit in HFrEF patients. **Methods:** Derivation and validation analyses were performed in $n=1,436$ total HF patients of European descent and with $EF < 50\%$. The PRP was derived in a random subset of the Henry Ford Pharmacogenomic Registry (HFPGR; $n=248$), and then validated in a meta-analysis of the remaining patients from HFPGR ($n=247$), the TIME-CHF ($n=431$), and HF-ACTION trial ($n=510$). The PRP was constructed from a genome-wide analysis of BB*genotype interaction predicting time to all-cause mortality, adjusted for MAGGIC score, genotype, level of BB exposure, and BB propensity score. **Results:** Five-fold cross-validation summaries out to 1000 SNPs identified optimal prediction with a 44 SNP score and cutoff at the 30th percentile. In validation testing ($n=1188$) greater BB exposure was associated with reduced all-cause mortality in patients with low-PRP score ($n=251$; $HR=0.19$ [95% $CI=0.04-0.51$], $p=0.0075$), but not high-PRP score ($n=937$; $HR=0.84$ [95% $CI=0.53-1.3$], $p=0.448$), a difference that was statistically significant (p interaction = 0.0235). Results were consistent regardless of atrial fibrillation, EF ($\leq 40\%$ vs. $41-50\%$), or when examining cardiovascular death. **Conclusions:** Among patients of European ancestry with HFrEF, a PRP distinguished patients who derived substantial survival benefit from BB exposure from a larger group that did not. Additional work is needed prospectively test clinical utility and to develop PRPs for other population groups and other medications.

Cardiology and Cardiovascular Research

Lee J, Chen T, and Gill E. Interventional echocardiography: Opportunities and challenges in an emerging field. *Echocardiography* 2020; Epub ahead of print. PMID: 33095471. [Full Text](#)

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The growth of transcatheter structural heart disease interventions has created a subspecialty of interventional imagers who focus on preprocedural planning and the periprocedural guidance of these complex cases. In particular interventional imagers who focus on periprocedural guidance have developed a specific expertise in interventional transesophageal echocardiography (iTEE). This nascent field has challenges in training, reimbursement, and occupational hazards which are unique to this field. This review encompasses the evolution of iTEE, current challenges, and future opportunities.

Cardiology and Cardiovascular Research

Nayak A, Hu Y, Ko YA, Mehta A, Liu C, Pennington J, Xie R, **Cowger J**, Kirklin JK, Kormos RL, Simon MA, and Morris AA. Gender Differences in Mortality After Left Ventricular Assist Device Implant: A Causal Mediation Analysis Approach. *Asaio j* 2020; Epub ahead of print. PMID: 33060408. [Full Text](#)

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We used the International Society for Heart and Lung Transplantation (ISHLT) Registry for Mechanically Assisted Circulatory Support (IMACS) database to examine 1) gender differences in post-left ventricular assist device (LVAD) mortality in the contemporary era and 2) preimplant clinical factors that might mediate any observed differences. Adults who received continuous-flow (CF)-LVAD from January 2013 to September 2017 (n = 9,565, age: 56.2 ± 13.2 years, 21.6% female, 31.1% centrifugal pumps) were analyzed. An inverse probability weighted Cox proportional hazards model was used to estimate association of female gender with all-cause mortality, adjusting for known covariates. Causal mediation analysis was performed to test plausible preimplant mediators mechanistically underlying any association between female gender and mortality. Females had higher mortality after LVAD (adjusted hazard ratio [HR]: 1.36; p < 0.0001), with significant gender × time interaction (p = 0.02). An early period of increased risk was identified, with females experiencing a higher risk of mortality during the first 4 months after implant (adjusted HR: 1.74; p < 0.0001), but not after (adjusted HR: 1.18; p = 0.16). More severe tricuspid regurgitation and smaller left ventricular end-diastolic diameter at baseline mediated ≈21.9% of the increased early hazard of death in females; however, most of the underlying mechanisms remain unexplained. Therefore, females have increased mortality only in the first 4 months after LVAD implantation, partially driven by worsening right ventricular dysfunction and LV-LVAD size mismatch.

Cardiology and Cardiovascular Research

O'Neill BP, Negrotto S, Yu D, Lakhter V, Depta J, McCabe JM, Dube S, Vaikom M, Wang DD, Patil P, Lindman B, Igleissis-Azuaje I, Fredi J, Lu X, and O'Neill WW. Caval Valve Implantation for Tricuspid Regurgitation: Insights From the United States Caval Valve Registry. *J Invasive Cardiol* 2020; Epub ahead of print. PMID: 33087585. [Request Article](#)

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BACKGROUND: We sought to describe the outcomes of patients who underwent caval valve implantation (CAVI) for treatment of severe tricuspid regurgitation (TR) in the United States. Previous studies on CAVI have used a variety of techniques and transcatheter valves. We present our findings from CAVI with inferior vena cava (IVC) implant only using a single valve. **METHODS:** Patients who were determined to be poor candidates for tricuspid valve surgery and underwent CAVI in the United States from March 1, 2013 through March 1, 2018 were included in this study. Data during hospitalizations and interim outpatient follow-up from each individual site were collected and entered into a central password-protected database. **RESULTS:** A total of 24 patients were treated. The median age was 79.5 years, 63% were women, and 96% were white. Twenty-three of 24 patients underwent valve implantation with a 29 mm Sapien 3 valve (Edwards Lifesciences). There was a 100% rate of successful valve implantation. There were no cases requiring emergency surgery. Thirty-day mortality rate was 25%. The median survival as of last follow-up of all patients was 350 days. Pre- and postprocedure New York Heart Association (NYHA) class data were available in 11 of 24 patients; of these 11 patients, 72.7% improved at least 1 NYHA class from baseline. **CONCLUSION:** CAVI may be performed safely in a high surgical risk population with severe tricuspid regurgitation. Dedicated studies with longer-term follow-up are needed.

Cardiology and Cardiovascular Research

Ramos-Rodriguez AJ, Cancel-Artau KJ, **Lemor A**, Carrasquillo OY, Lozano-Franco M, Santiago-Vazquez M, Barrera-Llaurador J, and Martin-Garcia RF. The in-hospital burden of dermatomyositis on patients with acute myocardial infarction: A nationwide cross-sectional analysis from 2004 to 2015. *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 33022307. [Full Text](#)

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Cardiology and Cardiovascular Research

Sabbah HN. Barth syndrome cardiomyopathy: targeting the mitochondria with elamipretide. *Heart Fail Rev* 2020; Epub ahead of print. PMID: 33001359. [Full Text](#)

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Barth syndrome (BTHS) is a rare, X-linked recessive, infantile-onset debilitating disorder characterized by early-onset cardiomyopathy, skeletal muscle myopathy, growth delay, and neutropenia, with a worldwide incidence of 1/300,000-400,000 live births. The high mortality rate throughout infancy in BTHS patients is related primarily to progressive cardiomyopathy and a weakened immune system. BTHS is caused by defects in the TAZ gene that encodes tafazzin, a transacylase responsible for the remodeling and maturation of the mitochondrial phospholipid cardiolipin (CL), which is critical to normal mitochondrial structure and function (i.e., ATP generation). A deficiency in tafazzin results in up to a 95% reduction in levels of structurally mature CL. Because the heart is the most metabolically active organ in the body, with the highest mitochondrial content of any tissue, mitochondrial dysfunction plays a key role in the development of heart failure in patients with BTHS. Changes in mitochondrial oxidative phosphorylation reduce the ability of mitochondria to meet the ATP demands of the human heart as well as skeletal muscle, namely ATP synthesis does not match the rate of ATP consumption. The presence of several cardiomyopathic phenotypes have been described in BTHS, including dilated cardiomyopathy, left ventricular noncompaction, either alone or in conjunction with other cardiomyopathic phenotypes, endocardial fibroelastosis, hypertrophic cardiomyopathy, and an apical form of hypertrophic

cardiomyopathy, among others, all of which can be directly attributed to the lack of CL synthesis, remodeling, and maturation with subsequent mitochondrial dysfunction. Several mechanisms by which these cardiomyopathic phenotypes exist have been proposed, thereby identifying potential targets for treatment. Dysfunction of the sarcoplasmic reticulum Ca(2+)-ATPase pump and inflammation potentially triggered by circulating mitochondrial components have been identified. Currently, treatment modalities are aimed at addressing symptomatology of HF in BTHS, but do not address the underlying pathology. One novel therapeutic approach includes elamipretide, which crosses the mitochondrial outer membrane to localize to the inner membrane where it associates with cardiolipin to enhance ATP synthesis in several organs, including the heart. Encouraging clinical results of the use of elamipretide in treating patients with BTHS support the potential use of this drug for management of this rare disease.

Cardiology and Cardiovascular Research

Samsky MD, Krucoff MW, Morrow DA, Abraham WT, Aguel F, Althouse AD, Chen E, Cigarroa JE, DeVore AD, Farb A, Gilchrist IC, Henry TD, Hochman JH, Kapur NK, Morrow V, Ohman EM, **O'Neill WW**, Piña IL, Proudfoot AG, Sapirstein JS, Seltzer JH, Senatore F, Shinnar M, Simonton CA, Tehrani BN, Thiele H, Truesdell AG, Waksman R, and Rao SV. Cardiac safety research consortium "shock II" think tank report: Advancing practical approaches to generating evidence for the treatment of cardiogenic shock. *Am Heart J* 2020; Epub ahead of print. PMID: 33011148. [Full Text](#)

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Cardiology and Cardiovascular Research

Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sørensen T, Böhm M, Bonderman D, Cleland JGF, Corbalan R, Crespo-Leiro MG, Dahlström U, Echeverria Correa LE, Fang JC, Filippatos G, Fonseca C, Goncalvesova E, Goudev AR, Howlett JG, **Lanfeard DE**, Lund M, Macdonald P, Mareev V, Momomura SI, O'Meara E, Parkhomenko A, Ponikowski P, Ramires FJA, Serpytis P, Sliwa K, Spinar J, Suter TM, Tomcsanyi J, Vandekerckhove H, Vinereanu D, Voors AA, Yilmaz MB, Zannad F, Sharpsten L, Legg JC, Abbasi SA, Varin C, Malik FI, and Kurtz CE. Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction: GALACTIC-HF baseline characteristics and comparison with contemporary clinical trials. *Eur J Heart Fail* 2020; Epub ahead of print. PMID: 32985088. [Full Text](#)

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AIMS: The safety and efficacy of the novel selective cardiac myosin activator, omecamtiv mecarbil, in patients with heart failure with reduced ejection fraction (HFrEF) is being tested in the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial. Here we describe the baseline characteristics of participants in GALACTIC-HF and how these compare with other contemporary trials. METHODS AND RESULTS: Adults with established HFrEF, New York Heart Association (NYHA) functional class \geq II, ejection fraction \leq 35%, elevated natriuretic peptides and either current hospitalization for heart failure or history of hospitalization/emergency department visit for heart failure within a year were randomized to either placebo or omecamtiv mecarbil (pharmacokinetic-guided dosing: 25, 37.5, or 50 mg bid). A total of 8256 patients [male (79%), non-white (22%), mean age 65 years] were enrolled with a mean ejection fraction 27%, ischaemic aetiology in 54%, NYHA class II 53% and III/IV 47%, and median N-terminal pro-B-type natriuretic peptide 1971 pg/mL. Heart failure therapies at baseline were among the most effectively employed in contemporary heart failure trials. GALACTIC-HF randomized patients representative of recent heart failure registries and trials with substantial numbers of patients also having characteristics understudied in previous trials including more from North America (n = 1386), enrolled as inpatients (n = 2084), systolic blood pressure <100 mmHg (n = 1127), estimated glomerular filtration rate <30 mL/min/1.73 m² (n = 528), and treated with sacubitril/valsartan at baseline (n = 1594). CONCLUSIONS: GALACTIC-HF enrolled a well-treated, high-risk population from both inpatient and outpatient settings, which will provide a definitive evaluation of the efficacy and safety of this novel therapy, as well as informing its potential future implementation.

Cardiology and Cardiovascular Research

Webb JG, Hensey M, Szerlip M, Schäfer U, Cohen GN, Kar S, Makkar R, Kipperman RM, Spargias K, **O'Neill WW**, Ng MKC, Fam NP, Rinaldi MJ, Smith RL, Walters DL, Raffel CO, Levisay J, Latib A, Montorfano M, Marcoff L, Shrivastava M, Boone R, Gilmore S, Feldman TE, and Lim DS. 1-Year Outcomes for Transcatheter Repair in Patients With Mitral Regurgitation From the CLASP Study. *JACC Cardiovasc Interv* 2020; 13(20):2344-2357. PMID: 33092709. [Full Text](#)

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OBJECTIVES: The authors report the CLASP (Edwards PASCAL Transcatheter Mitral Valve Repair System Study) expanded experience, 1-year outcomes, and analysis by functional mitral regurgitation (FMR) and degenerative mitral regurgitation (DMR). **BACKGROUND:** The 30-day results from the CLASP study of the PASCAL transcatheter valve repair system for clinically significant mitral regurgitation (MR) have been previously reported. **METHODS:** Eligible patients had symptomatic MR $\geq 3+$, were receiving optimal medical therapy, and were deemed candidates for transcatheter mitral repair by the local heart team. Primary endpoints included procedural success, clinical success, and major adverse event rate at 30 days. Follow-up was continued to 1 year. **RESULTS:** One hundred nine patients were treated (67% FMR, 33% DMR); the mean age was 75.5 years, and 57% were in New York Heart Association functional class III or IV. At 30 days, there was 1 cardiovascular death (0.9%), MR $\leq 1+$ was achieved in 80% of patients (77% FMR, 86% DMR) and MR $\leq 2+$ in 96% (96% FMR, 97% DMR), 88% of patients were in New York Heart Association functional class I or II, 6-min walk distance had improved by 28 m, and Kansas City Cardiomyopathy Questionnaire score had improved by 16 points ($p < 0.001$ for all). At 1 year, Kaplan-Meier survival was 92% (89% FMR 96% DMR) with 88% freedom from heart failure hospitalization (80% FMR, 100% DMR), MR was $\leq 1+$ in 82% of patients (79% FMR, 86% DMR) and $\leq 2+$ in 100% of patients, 88% of patients were in New York Heart Association functional class I or II, and Kansas City Cardiomyopathy Questionnaire score had improved by 14 points ($p < 0.001$ for all). **CONCLUSIONS:** The PASCAL transcatheter valve repair system demonstrated a low complication rate and high survival, with robust sustained MR reduction accompanied by significant improvements in functional status and quality of life at 1 year. (The CLASP Study Edwards PASCAL Transcatheter Mitral Valve Repair System Study [CLASP]; NCT03170349).

Center for Individualized and Genomic Medicine Research

Bick AG, Weinstock JS, Nandakumar SK, Fulco CP, Bao EL, Zekavat SM, Szeto MD, Liao X, Leventhal MJ, Nasser J, Chang K, Laurie C, Burugula BB, Gibson CJ, Lin AE, Taub MA, Aguet F, Ardlie K, Mitchell BD, Barnes KC, Moscati A, Fornage M, Redline S, Psaty BM, Silverman EK, Weiss ST, Palmer ND,

Vasan RS, Burchard EG, Kardina SLR, He J, Kaplan RC, Smith NL, Arnett DK, Schwartz DA, Correa A, de Andrade M, Guo X, Konkole BA, Custer B, Peralta JM, **Gui H**, Meyers DA, McGarvey ST, Chen IY, Shoemaker MB, Peyser PA, Broome JG, Gogarten SM, Wang FF, Wong Q, Montasser ME, Daya M, Kenny EE, North KE, Launer LJ, Cade BE, Bis JC, Cho MH, Lasky-Su J, Bowden DW, Cupples LA, Mak ACY, Becker LC, Smith JA, Kelly TN, Aslibekyan S, Heckbert SR, Tiwari HK, Yang IV, Heit JA, Lubitz SA, Johnsen JM, Curran JE, Wenzel SE, Weeks DE, Rao DC, Darbar D, Moon JY, Tracy RP, Butth EJ, Rafaels N, Loos RJF, Durda P, Liu Y, Hou L, Lee J, Kachroo P, Freedman BI, Levy D, Bielak LF, Hixson JE, Floyd JS, Whitsel EA, Ellinor PT, Irvin MR, Fingerlin TE, Raffield LM, Armasu SM, Wheeler MM, Sabino EC, Blangero J, Williams LK, Levy BD, Sheu WH, Roden DM, Boerwinkle E, Manson JE, Mathias RA, Desai P, Taylor KD, Johnson AD, Auer PL, Kooperberg C, Laurie CC, Blackwell TW, Smith AV, Zhao H, Lange E, Lange L, Rich SS, Rotter JI, Wilson JG, Scheet P, Kitzman JO, Lander ES, Engreitz JM, Ebert BL, Reiner AP, Jaiswal S, Abecasis G, Sankaran VG, Kathiresan S, and Natarajan P. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature* 2020; Epub ahead of print. PMID: 33057201. [Full Text](#)

Age is the dominant risk factor for most chronic human diseases, but the mechanisms through which ageing confers this risk are largely unknown(1). The age-related acquisition of somatic mutations that lead to clonal expansion in regenerating haematopoietic stem cell populations has recently been associated with both haematological cancer(2-4) and coronary heart disease(5)-this phenomenon is termed clonal haematopoiesis of indeterminate potential (CHIP)(6). Simultaneous analyses of germline and somatic whole-genome sequences provide the opportunity to identify root causes of CHIP. Here we analyse high-coverage whole-genome sequences from 97,691 participants of diverse ancestries in the National Heart, Lung, and Blood Institute Trans-omics for Precision Medicine (TOPMed) programme, and identify 4,229 individuals with CHIP. We identify associations with blood cell, lipid and inflammatory traits that are specific to different CHIP driver genes. Association of a genome-wide set of germline genetic variants enabled the identification of three genetic loci associated with CHIP status, including one locus at TET2 that was specific to individuals of African ancestry. In silico-informed in vitro evaluation of the TET2 germline locus enabled the identification of a causal variant that disrupts a TET2 distal enhancer, resulting in increased self-renewal of haematopoietic stem cells. Overall, we observe that germline genetic variation shapes haematopoietic stem cell function, leading to CHIP through mechanisms that are specific to clonal haematopoiesis as well as shared mechanisms that lead to somatic mutations across tissues.

Center for Individualized and Genomic Medicine Research

Lanfeer DE, Luzum JA, She R, Gui H, Donahue MP, O'Connor CM, Adams KF, Sanders-van Wijk S, Zeld N, Maeder MT, Sabbah HN, Kraus WE, Brunner-La Rocca HP, Li J, and Williams LK. Polygenic Score for Beta-Blocker Survival Benefit in European Ancestry Patients with Reduced Ejection Fraction Heart Failure. *Circ Heart Fail* 2020; Epub ahead of print. PMID: 33012170. [Full Text](#)

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Background: Beta-blockers (BB) are mainstay therapy for heart failure with reduced ejection fraction (HFrEF). However, individual patient responses to BB vary, which may be partially due to genetic variation. The goal of this study was to derive and validate the first polygenic response predictor (PRP) for BB survival benefit in HFrEF patients. Methods: Derivation and validation analyses were performed in n=1,436 total HF patients of European descent and with EF <50%. The PRP was derived in a random subset of the Henry Ford Pharmacogenomic Registry (HFPGR; n=248), and then validated in a meta-analysis of the remaining patients from HFPGR (n=247), the TIME-CHF (n=431), and HF-ACTION trial (n=510). The PRP was constructed from a genome-wide analysis of BB*genotype interaction predicting time to all-cause mortality, adjusted for MAGGIC score, genotype, level of BB exposure, and BB propensity score. Results: Five-fold cross-validation summaries out to 1000 SNPs identified optimal prediction with a 44 SNP score and cutoff at the 30th percentile. In validation testing (n=1188) greater BB exposure was associated with reduced all-cause mortality in patients with low-PRP score (n=251; HR=0.19 [95% CI=0.04-0.51], p=0.0075), but not high-PRP score (n=937; HR=0.84 [95% CI=0.53-1.3], p=0.448), a difference that was statistically significant (p interaction =0.0235). Results were consistent regardless of atrial fibrillation, EF ($\leq 40\%$ vs. 41-50%), or when examining cardiovascular death. Conclusions: Among patients of European ancestry with HFrEF, a PRP distinguished patients who derived substantial survival benefit from BB exposure from a larger group that did not. Additional work is needed prospectively test clinical utility and to develop PRPs for other population groups and other medications.

Dermatology

Zouboulis CC, Benhadou F, Byrd AS, Chandran NS, Giamarellos-Bourboulis EJ, Fabbrocini G, Frew JW, Fujita H, González-López MA, Guillem P, Gulliver WPF, **Hamzavi I**, Hayran Y, Hórvath B, Hùe S, Hunger RE, Ingram JR, Jemec GBE, Ju Q, Kimball AB, Kirby JS, Konstantinou MP, Lowes MA, MacLeod AS, Martorell A, Marzano AV, Matusiak Ł, Nassif A, Nikiphorou E, Nikolakis G, Nogueira da Costa A, Okun MM, Orenstein LAV, Pascual JC, Paus R, Perin B, Prens EP, Röhn TA, Szegedi A, Szepletowski JC, Tzellos T, Wang B, and van der Zee HH. What causes hidradenitis suppurativa ? - 15 years after. *Exp Dermatol* 2020; Epub ahead of print. PMID: 33058306. [Full Text](#)

The 14 authors of the first review article on hidradenitis suppurativa (HS) pathogenesis published 2008 in EXPERIMENTAL DERMATOLOGY cumulating from the 1(st) International Hidradenitis Suppurativa Research Symposium held March 30-April 2, 2006 in Dessau, Germany with 33 participants were prophetic when they wrote "Hopefully, this heralds a welcome new tradition: to get to the molecular heart of HS pathogenesis, which can only be achieved by a renaissance of solid basic HS research, as the key to developing more effective HS therapy." (Kurzen et al. What causes hidradenitis suppurativa?. *Exp Dermatol* 2008;17:455). Fifteen years later, there is no doubt that the wished renaissance of solid basic HS research is ongoing with rapid steps and that HS has developed deep roots among inflammatory diseases in Dermatology and beyond, recognized as "the only inflammatory skin disease than can be healed". This anniversary article of 43 research-performing authors from all around the globe in the official journal of the European Hidradenitis Suppurativa Foundation e.V. (EHSF e.V.) and the Hidradenitis Suppurativa Foundation, Inc. (HSF USA) summarizes the evidence of the intense HS clinical and experimental research during the last 15 years in all aspects of the disease and provides information of the developments to come in the near future.

Diagnostic Radiology

Boregowda U, Gandhi D, Jain N, **Khanna K**, and Gupta N. Comprehensive Literature Review and Evidence evaluation of Experimental Treatment in COVID 19 Contagion. *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine* 2020; 14. PMID: Not assigned. [Full Text](#)

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Importance: Coronavirus 2019 pandemic (COVID 19) is caused by the Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) virus. The pandemic is affecting the livelihood of millions of people all over the world. At the time of preparing this report, the pandemic has affected 1 827 284

patients, with 113 031 deaths in 185 countries as per Johns Hopkins University. With no proven treatment for the disease, prevention of the disease in the community and healthcare setting is need of the hour. Objective: To perform a comprehensive literature search for preventive measures and experimental treatment options. In this review, we have focused our discussion on the risk of disease transmission, supportive treatment, and possible treatment options based on available evidence. Evidence Review: We performed a literature search on google scholar, PubMed, and society guidelines for literature related to COVID 19 and previous coronavirus pandemics. We included data review articles, observational studies, and controlled trials to synthesize the treatment options for COVID 19. Findings: In this article, we have extensively reviewed and discussed recommendations from various world organizations for the public and healthcare workers. We have also discussed currently available experimental treatments since there is no proven treatment for COVID 19. The best method of dealing with the current outbreak is to reduce the community spread and thus “flatten the curve.” Although Hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir, and Azithromycin have been tried, passive immunity through convalescent serum and vaccine is still at an experimental stage. Patients with severe COVID 19 infections could be considered for this experimental treatment through various national randomized control trials, which may eventually lead to an evidence-based treatment strategy. Conclusions and Relevance: Awareness of currently available experimental treatment among healthcare providers and exploration of possible treatment options through evidence is need of the hour. We have discussed the most recently available literature and evidence behind experimental treatment in this article.

Diagnostic Radiology

Oravec D, Zael R, Flynn MJ, and Yeni YN. Vertebral stiffness measured via tomosynthesis-based digital volume correlation is strongly correlated with reference values from micro-CT-based DVC. *Med Eng Phys* 2020; 84:169-173. PMID: 32977915. [Full Text](#)

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Digital tomosynthesis (DTS) is a clinically available modality that allows imaging of a patient's spine in supine and standing positions. The purpose of this study was to establish the extent to which vertebral displacement and stiffness derived from DTS-based digital volume correlation (DTS-DVC) are correlated with those from a reference method, i.e., microcomputed tomography-based DVC (μ CT-DVC). T11 vertebral bodies from 11 cadaveric donors were DTS imaged twice in a nonloaded state and once under a fixed load level approximating upper body weight. The same vertebrae were μ CT imaged in nonloaded and loaded states (40 μ m voxel size). Vertebral displacements were calculated at each voxel using DVC with pairs of nonloaded and loaded images, from which endplate-to-endplate axial displacement (D(DVC)) and vertebral stiffness (S(DVC)) were calculated. Both D(DVC) and S(DVC) demonstrated strong positive correlations between DTS-DVC and μ CT-DVC, with correlations being stronger when vertebral displacement was calculated using the median ($R(2)=0.80$; $p<0.0002$ and $R(2)=0.93$; $p<0.0001$, respectively) rather than average displacement ($R(2)=0.63$; $p<0.004$ and $R(2)=0.69$; $p<0.002$, respectively). In conclusion, the demonstrated relationship of DTS-DVC with the μ CT standard supports further development of a biomechanics-based clinical assessment of vertebral bone quality using the DTS-DVC technique.

Diagnostic Radiology

Poyiadji N, Klochko C, LaForce J, Brown ML, and Griffith B. COVID-19 and Radiology Resident Imaging Volumes-Differential Impact by Resident Training Year and Imaging Modality. *Acad Radiol* 2020; Epub ahead of print. PMID: 33046369. [Full Text](#)

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RATIONALE AND OBJECTIVES: The COVID-19 pandemic has greatly impacted radiology departments across the country. The pandemic has also disrupted resident education, both due to departmental social distancing efforts and reduced imaging volumes. The purpose of this study was to assess the differential impact the pandemic had on radiology resident imaging volumes by training year and imaging modality. **MATERIALS AND METHODS:** All signed radiology resident reports were curated during defined pre-pandemic and intrapandemic time periods. Imaging case volumes were analyzed on a mean per resident basis to quantify absolute and percent change by training level. Change in total volume by imaging modality was also assessed. The number of resident workdays assigned outside the normal reading room was also calculated. **RESULTS:** Overall percent decline in resident imaging interpretation volume from the pre-pandemic to intrapandemic time period was 62.8%. R1s and R2s had the greatest decline at 87.3% and 64.3%, respectively. Mammography, MRI and nuclear medicine had the greatest decline in resident interpretation volume at 92.0%, 73.2%, and 73.0%, respectively. During the intrapandemic time period, a total of 478 resident days (mean of 14.5 days per resident) were reassigned outside of the radiology reading room. **CONCLUSION:** The COVID-19 pandemic caused a marked decrease in radiology resident imaging interpretation volume and has had a tremendous impact on resident education. The decrease in case interpretation, as well as in-person teaching has profound implications for resident education. Knowledge of this differential decrease by training level will help residency programs plan for the future.

Gastroenterology

Gonzalez H, Imam Z, Wong R, **Li J, Lu M, Trudeau S, Gordon S,** Imam M, and Gish R. Normal alkaline phosphatase levels are dependent on race/ethnicity: National GEP Health and Nutrition Examination Survey data. *BMJ Open Gastroenterol* 2020; 7(1). PMID: 33055108. [Full Text](#)

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OBJECTIVE: The range of normal serum alkaline phosphatase is not well defined. We used data from the National Health and Nutrition Examination Survey from 2009 to 2016 to generate normal ranges for a racially diverse sample of healthy adults. **METHODS:** Respondents 18 years or older were included. Conditions known to elevate alkaline phosphatase were cause for exclusion. Alkaline phosphatase was measured using a colorimetric method based on standardised National Health and Nutrition Examination Survey protocols. Because alkaline phosphatase values were not normally distributed, log transformation was used. We calculated upper limits of normal (97.5 percentile), stratified by sex and race/ethnicity, and 90% CIs for the upper limits of normal. **RESULTS:** 1199 respondents (673 female, 526 male) had body mass index from 18.5 to less than 25. Upper limits of normal were highest among Hispanics (123.2 IU/L (90% CI 110.2 to 136.7) for females; 123.8 IU/L (90% CI 112.0 to 135.1) for males), followed by African Americans (109.9 IU/L (90% CI 97.3 to 122.4) for females; 116.3 IU/L (90% CI 105.0 to 126.1) for males) and whites (97.1 IU/L (90% CI 91.0 to 103.4) for females; 109.6 IU/L (90% CI 102.1 to 116.3) for males). Asian American/Pacific Islander respondents had the lowest results: 93.8 IU/L (90% CI 88.2 to 99.5) for females and 95.3 IU/L (90% CI 88.1 to 102.1) for males. **CONCLUSIONS:** The upper limit of normal alkaline phosphatase varies by race/ethnicity in a large US sample with body mass index of 18.5<25.

Gastroenterology

Kitajima T, Shamaa T, Hibi T, **Moonka D,** Sapisochin G, **Abouljoud MS,** and **Nagai S.** Response to: "Surgical Volume Alone Does Not Determine Outcome Following Liver Transplant for Perihilar Cholangiocarcinoma". *Ann Surg Oncol* 2020; Epub ahead of print. PMID: 33063257. [Full Text](#)

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Gastroenterology

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The liver transplantation (LT) population is aging, with the need for transplant being driven by the growing prevalence of nonalcoholic steatohepatitis (NASH). Older LT recipients with NASH may be at an increased risk for adverse outcomes after LT. Our objective is to characterize outcomes in these recipients in a large multicenter cohort. All primary LT recipients ≥ 65 years from 2010 to 2016 at 13 centers in the Re-Evaluating Age Limits in Transplantation (REALT) consortium were included. Of 1023 LT recipients, 226 (22.1%) were over 70 years old, and 207 (20.2%) had NASH. Compared with other LT recipients, NASH recipients were older (68.0 versus 67.3 years), more likely to be female (47.3% versus 32.8%), White (78.3% versus 68.0%), Hispanic (12.1% versus 9.2%), and had higher Model for End-Stage Liver Disease-sodium (21 versus 18) at LT ($P < 0.05$ for all). Specific cardiac risk factors including diabetes with or without chronic complications (69.6%), hypertension (66.3%), hyperlipidemia (46.3%), coronary artery disease (36.7%), and moderate-to-severe renal disease (44.4%) were highly prevalent among NASH LT recipients. Graft survival among NASH patients was 90.3% at 1 year and 82.4% at 3 years compared with 88.9% at 1 year and 80.4% at 3 years for non-NASH patients (log-rank $P = 0.58$ and $P = 0.59$, respectively). Within 1 year after LT, the incidence of graft rejection (17.4%), biliary strictures (20.9%), and solid organ cancers (4.9%) were comparable. Rates of cardiovascular (CV) complications, renal failure, and infection were also similar in both groups. We observed similar posttransplant morbidity and mortality outcomes for NASH and non-NASH LT recipients. Certain CV risk factors were more prevalent in this population, although posttransplant outcomes within 1 year including CV events and renal failure were similar to non-NASH LT recipients.

Gastroenterology

Solanki S, Chakinala RC, **Haq KF**, Singh J, Khan MA, Solanki D, Vyas MJ, Kichloo A, Mansuri U, Shah H, Patel A, Haq KS, Iqbal U, Nabors C, Khan HMA, and Aronow WS. Paralytic ileus in the United States: A cross-sectional study from the national inpatient sample. *SAGE Open Med* 2020; 8. PMID: 33088567.

[Full Text](#)

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INTRODUCTION: Paralytic ileus is a common clinical condition leading to significant morbidity and mortality. Most studies to date have focused on postoperative ileus, a common but not exclusive cause of the condition. There are limited epidemiological data regarding the incidence and impact of paralytic ileus and its relationship to other clinical conditions. In this cross-sectional study, we analyzed national inpatient hospitalization trends, demographic variation, cost of care, length of stay, and mortality for paralytic ileus hospitalizations as a whole. **METHODS:** The National Inpatient Sample database was used to identify all hospitalizations with the diagnosis of paralytic ileus (International Classification of Diseases, 9th Revision code 560.1) as primary or secondary diagnosis during the period from 2001 to 2011. Statistical analysis was performed using Cochran-Armitage trend test, Wilcoxon rank sum test, and Poisson regression. **RESULTS:** In 2001, there were 362,561 hospitalizations with the diagnosis of paralytic ileus as compared to 470,110 in 2011 ($p < 0.0001$). The age group 65-79 years was most commonly affected by paralytic ileus throughout the study period. In-hospital all-cause mortality decreased from 6.03% in 2001 to 5.10% in 2011 ($p < 0.0001$). However, the average cost of care per hospitalization increased from US\$19,739 in 2001 to US\$26,198 in 2011 (adjusted for inflation, $p < 0.0001$). **CONCLUSION:** There was a significant rise in the number of hospitalizations of paralytic ileus with increased cost of care and reduced all-cause mortality.

Global Health Initiative

Imran Khan M, Aijaz S, Syed FF, and **Kaljee L**. An optimal typhoid conjugate vaccine coverage complemented with WASH is imperative for the control of antimicrobial resistance in Pakistan. *Vaccine* 2020; 38(45):6969-6970. PMID: 33008669. [Full Text](#)

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Hematology/Oncology

Apolo AB, Ellerton JA, Infante JR, Agrawal M, Gordon MS, Aljumaily R, Gourdin T, Dirix L, Lee KW, Taylor MH, Schöffski P, **Wang D**, Ravaud A, Manitz J, Pennock G, Ruisi M, Gulley JL, and Patel MR. Avelumab as second-line therapy for metastatic, platinum-treated urothelial carcinoma in the phase Ib JAVELIN Solid Tumor study: 2-year updated efficacy and safety analysis. *J Immunother Cancer* 2020; 8(2). PMID: 33037118. [Full Text](#)

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BACKGROUND: Anti-programmed cell death ligand 1 (PD-L1)/programmed cell death 1 antibodies have shown clinical activity in platinum-treated metastatic urothelial carcinoma, resulting in regulatory approval of several agents, including avelumab (anti-PD-L1). We report ≥ 2 -year follow-up data for avelumab treatment and exploratory subgroup analyses in patients with urothelial carcinoma. **METHODS:** Patients with previously treated advanced/metastatic urothelial carcinoma, pooled from two cohorts of the phase Ib JAVELIN Solid Tumor trial, received avelumab 10 mg/kg every 2 weeks until disease progression, unacceptable toxicity or withdrawal. End points included best overall response and progression-free survival (PFS) per RECIST V.1.1, overall survival (OS) and safety. Post hoc analyses included objective response rates (ORRs) in subgroups defined by established high-risk/poor-prognosis characteristics and association between time to response and outcome. **RESULTS:** 249 patients received avelumab; efficacy was assessed in 242 postplatinum patients. Median follow-up was 31.9 months (range 24-43), and median treatment duration was 2.8 months (range 0.5-42.8). The confirmed ORR was 16.5% (95% CI 12.1% to 21.8%; complete response in 4.1% and partial response in 12.4%). Median duration of response was 20.5 months (95% CI 9.7 months to not estimable). Median PFS was 1.6 months (95% CI 1.4 to 2.7 months) and the 12-month PFS rate was 16.8% (95% CI 11.9% to 22.4%). Median OS was 7.0 months (95% CI 5.9 to 8.5 months) and the 24-month OS rate was 20.1% (95% CI 15.2% to 25.4%). In post hoc exploratory analyses, avelumab showed antitumor activity in high-risk subgroups, including elderly patients and those with renal insufficiency or upper tract disease; ORRs were numerically lower in patients with liver metastases or low albumin levels. Objective response achieved by 3 months versus later was associated with longer OS (median not reached (95% CI 18.9 months to not estimable) vs 7.1 months (95% CI 5.2 to 9.0 months)). Safety findings were consistent with previously reported 6-month analyses. **CONCLUSIONS:** After ≥ 2 years of follow-up, avelumab showed prolonged efficacy and acceptable safety in patients with platinum-treated advanced/metastatic urothelial carcinoma, including high-risk subgroups. Survival appeared longer in patients who responded within 3 months. Long-term safety findings were consistent with earlier reports with avelumab treatment in this patient population.

Hematology/Oncology

Jänne PA, **Rybkin II**, Spira AI, Riely GJ, Papadopoulos KP, Sabari JK, Johnson ML, Heist RS, Bazhenova L, Barve M, Pacheco JM, Leal TA, Velastegui K, Cornelius C, Olson P, Christensen JG, Kheoh T, Chao RC, and Ou SHI. KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Advanced/Metastatic Non–Small-Cell Lung Cancer (NSCLC) Harboring KRAS G12C Mutation. *European Journal of Cancer* 2020; 138:S1-S2. PMID: Not assigned. [Full Text](#)

Hematology/Oncology

Johnson ML, Ou SHI, Barve M, **Rybkin II**, Papadopoulos KP, Leal TA, Velastegui K, Christensen JG, Kheoh T, Chao RC, and Weiss J. KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients with Colorectal Cancer (CRC) and Other Solid Tumors Harboring a KRAS G12C Mutation. *European Journal of Cancer* 2020; 138:S2. PMID: Not assigned. [Full Text](#)

Hypertension and Vascular Research

Hamid S, Rhaleb IA, Kassem KM, and **Rhaleb NE**. Role of Kinins in Hypertension and Heart Failure. *Pharmaceuticals (Basel)* 2020; 13(11). PMID: 33126450. [Full Text](#)

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The kallikrein-kinin system (KKS) is proposed to act as a counter regulatory system against the vasopressor hormonal systems such as the renin-angiotensin system (RAS), aldosterone, and catecholamines. Evidence exists that supports the idea that the KKS is not only critical to blood pressure but may also oppose target organ damage. Kinins are generated from kininogens by tissue and plasma kallikreins. The putative role of kinins in the pathogenesis of hypertension is discussed based on human mutation cases on the KKS or rats with spontaneous mutation in the kininogen gene sequence and mouse models in which the gene expressing only one of the components of the KKS has been deleted or over-expressed. Some of the effects of kinins are mediated via activation of the B(2) and/or B(1) receptor and downstream signaling such as eicosanoids, nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF) and/or tissue plasminogen activator (T-PA). The role of kinins in blood pressure regulation at normal or under hypertension conditions remains debatable due to contradictory reports from various laboratories. Nevertheless, published reports are consistent on the protective and mediating roles of kinins against ischemia and cardiac preconditioning; reports also demonstrate the roles of kinins in the cardiovascular protective effects of the angiotensin-converting enzyme (ACE) and angiotensin type 1 receptor blockers (ARBs).

Hypertension and Vascular Research

Mottillo EP, and Steinberg GR. Current and emerging roles of adipose tissue in health and disease. *Biochem J* 2020; 477(19):3645-3647. PMID: 33017469. [Full Text](#)

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Infectious Diseases

Fram G, Wang DD, Malette K, Villablanca P, Kang G, So K, Basir MB, Khan A, McKinnon JE, Zervos M, and O'Neill WW. Cardiac Complications Attributed to Hydroxychloroquine: A systematic review of the Literature Pre-COVID-19. *Curr Cardiol Rev* 2020; Epub ahead of print. PMID: 33059567.

[Request Article](#)

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INTRODUCTION: Hydroxychloroquine has been used for rheumatological diseases for many decades and is considered a safe medication. With the COVID-19 outbreak, there has been an increase in reports associating cardiotoxicity with hydroxychloroquine. It is unclear if cardiotoxic profile of hydroxychloroquine is previously underreported in the literature, or a new manifestation of COVID-19 and therapeutic interventions. This manuscript evaluates the incidence of cardiotoxicity associated with hydroxychloroquine prior to onset of COVID-19. **METHODS:** PubMed, EMBASE, and Cochrane databases were searched for keywords derived from MeSH terms, prior to 4/9/2020. Inclusion eligibility was based on appropriate reporting of cardiac conditions and study design. **RESULTS:** Sixty-nine articles were identified (58 case reports, 11 case series). Majority (84%) of patients were female, with a median age of 49.2 (range 16-92) years. Fifteen of 185 patients with cardiotoxic events were in the setting of acute intentional overdose. In acute overdose, the median ingestion was 17,857 \pm 14,873 mg. Two of 15 patients died after acute intoxication. In patients with long-term hydroxychloroquine use (10.5 \pm 8.9 years), new onset systolic heart failure occurred in 54 of 155 patients (35%) with median cumulative ingestion of 1,493,800 \pm 995,517 mg. The majority of patients improved with withdrawal of hydroxychloroquine and standard therapy. **CONCLUSIONS:** Millions of hydroxychloroquine doses are prescribed annually. Prior to COVID-19 pandemic, cardiac complications attributed to hydroxychloroquine were uncommon. Further studies are needed to understand the impact of COVID-19 on the cardiovascular system to understand presence or absence of potential medication interactions with hydroxychloroquine in this new pathophysiological state.

Infectious Diseases

Shallal A, Kenney R, and Weinmann A. Missed Vaccine Opportunities to *S. pneumoniae* and Influenza in Patients Admitted During the COVID-19 Pandemic. *Infect Control Hosp Epidemiol* 2020; Epub ahead of print. PMID: 33100230. [Full Text](#)

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Infectious Diseases

Shallal A, Markowitz N, and Tibbetts R. The Brief Case: Cough in an Immunocompromised Patient. *J Clin Microbiol* 2020; 58(11). PMID: 33087542. [Full Text](#)

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Infectious Diseases

Shallal A, Markowitz N, and Tibbetts R. Closing the Brief Case: Cough in an Immunocompromised Patient. *J Clin Microbiol* 2020; 58(11). PMID: 33087543. [Full Text](#)

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Infectious Diseases

Vaughn VM, O'Malley M, Flanders SA, Gandhi TN, Petty LA, Malani AN, **Weinmann A**, Horowitz JK, and Chopra V. Association of Infectious Disease Physician Approval of Peripherally Inserted Central Catheter With Appropriateness and Complications. *JAMA Netw Open* 2020; 3(10):e2017659. PMID: 33084898. [Full Text](#)

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IMPORTANCE: Peripherally inserted central catheters (PICCs) are frequently used to deliver intravenous antimicrobial therapy. However, inappropriate PICC use may lead to patient harm. **OBJECTIVE:** To evaluate whether infectious disease physician approval prior to PICC placement for intravenous antimicrobials is associated with more appropriate device use and fewer complications. **DESIGN, SETTING, AND PARTICIPANTS:** This cohort study of 21 653 PICCs placed for a primary indication of intravenous antimicrobial therapy between January 1, 2015, and July 26, 2019, was conducted in 42 hospitals participating in a quality collaborative across Michigan among hospitalized medical patients. **MAIN OUTCOMES AND MEASURES:** Appropriateness of PICCs was defined according to the Michigan Appropriateness Guide for Intravenous Catheters as a composite measure of (1) single-lumen catheter use, (2) avoiding use of PICCs for 5 days or less, and (3) avoiding use of PICCs for patients with chronic kidney disease (defined as an estimated glomerular filtration rate <45 mL/min/1.73 m²). Complications related to PICCs included catheter occlusion, deep vein thrombosis, and central line-associated bloodstream infection. The association between infectious disease physician approval, device appropriateness, and catheter complications was assessed using multivariable models, adjusted for patient comorbidities and hospital clustering. Results were expressed as odds ratios with 95% CIs. **RESULTS:** A total of 21 653 PICCs were placed for intravenous antimicrobials (11 960 PICCs were placed in men [55.2%]; median age, 64.5 years [interquartile range, 53.4-75.4 years]); 10 238 PICCs (47.3%) were approved by an infectious disease physician prior to placement. Compared with PICCs with no documented approval, PICCs with approval by an infectious disease physician were more likely to be appropriately used (72.7% [7446 of 10 238] appropriate with approval vs 45.4% [5180 of 11 415] appropriate without approval; odds ratio, 3.53; 95% CI, 3.29-3.79; P < .001). Furthermore, approval was associated with lower odds of a PICC-related complication (6.5% [665 of 10 238] with approval vs 11.3% [1292 of 11 415] without approval; odds ratio, 0.55; 95% CI, 0.50-0.61). **CONCLUSIONS AND RELEVANCE:** This cohort study suggests that, when PICCs were placed for intravenous antimicrobial therapy, infectious disease physician approval of PICC insertion was associated with more appropriate device use and fewer complications. Policies aimed at ensuring infectious disease physician approval prior to PICC placement for antimicrobials may improve patient safety.

Internal Medicine

Al-Darzi WK, Hana A, Lahiri MK, Dagher C, Greenberg JC, Alaswad K, Rabbani BT, McCord JK, and Reddy M. Diffuse B Cell Lymphoma Leading to Complete Heart Block: Is This Transient or Permanent? *Am J Case Rep* 2020; 21. PMID: 33093439. [Request Article](#)

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BACKGROUND Cardiac lymphomas can lead to heart block through tumor disruption of the cardiac conduction system. It is reported that with cardiac tumor treatment, conduction abnormalities can resolve. We present a case of cardiac lymphoma resulting in complete heart block requiring a pacemaker, followed by reduction of the pacing burden after chemotherapy. **CASE REPORT** A 72-year-old woman with a medical history of hypertension, hypothyroidism, and persistent atrial fibrillation presented with dyspnea on exertion and fatigue for 2 weeks. Electrocardiography revealed complete heart block with junctional bradycardia of 48 beats per min. Transthoracic echocardiography demonstrated preserved left ventricular systolic function along with a large mass (3.6x3.7 cm). An endomyocardial biopsy was consistent with diffuse large B cell lymphoma, and the cardiac involvement was thought to be secondary based on positron emission tomography scan findings. Her clinical course was complicated by an episode

of syncope deemed to be due to transient asystole, and an urgent single-chamber permanent pacemaker was implanted. Chemotherapy was initiated with R-CHOP, and, following the second cycle of chemotherapy, a positron emission tomography scan revealed no increased radiotracer uptake and thus resolution of all tumors. An echocardiogram 6 weeks after chemotherapy showed complete resolution of the cardiac mass. Subsequent serial pacemaker checks demonstrated improvement of atrioventricular nodal function as manifested by reduced pacing burden. **CONCLUSIONS** Lymphoma with cardiac involvement can lead to conduction abnormalities, including CHB, and heart block in the setting of these tumors may be reversible with appropriate therapy; however, implantation of a pacemaker remains inevitable in some cases.

Internal Medicine

Barssoum K, **Altibi AM**, Rai D, Kharsa A, Kumar A, Chowdhury M, Elkaryoni A, Abuzaid AS, Baibhav B, Parikh V, Masri A, Amsallem M, and Nanda NC. Assessment of right ventricular function following left ventricular assist device (LVAD) implantation-The role of speckle-tracking echocardiography: A meta-analysis. *Echocardiography* 2020; Epub ahead of print. PMID: 33084128. [Full Text](#)

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BACKGROUND: Right ventricular failure (RVF) following left ventricular assist device (LVAD) implantation is associated with worse outcomes. Prediction of RVF is difficult with routine transthoracic echocardiography (TTE), while speckle-tracking echocardiography (STE) showed promising results. We performed systematic review and meta-analysis of published literature. **METHODS:** We queried multiple databases to compile articles reporting preoperative or intraoperative right ventricle global longitudinal strain (RVGLS) or right ventricle free wall strain (RVFWS) in LVAD recipients. The standard mean difference (SMD) in RVGLS and RVFWS in patients with and without RVF postoperatively was pooled using random-effects model. **RESULTS:** Seventeen studies were included. Patients with RVF had significantly lower RVGLS and RVFWS as compared to non-RVF patients; SMD: 2.79 (95% CI: -4.07 to -1.50; P: <.001) and -3.05 (95% CI: -4.11 to -1.99; P: <.001), respectively. The pooled odds ratio (OR) for RVF per percentage increase of RVGLS and RVFWS were 1.10 (95% CI: 0.98-1.25) and 1.63 (95% CI 1.07-2.47), respectively. In a subgroup analysis, TTE-derived GLS and FWS were significantly lower in RVF patients as compared to non-RVF patients; SMD of -3.97 (95% CI: -5.40 to -2.54; P: <.001) and -3.05 (95% CI: -4.11 to -1.99; P: <.001), respectively. There was no significant difference between RVF and non-RVF groups in TEE-derived RVGLS and RVFWS. **CONCLUSION:** RVGLS and RVFWS were lower in patients who developed RVF as compared to non-RVF patients. In a subgroup analysis, TTE-derived RVGLS and RVFWS were reduced in RVF patients as compared to non-RVF patients. This difference was not reported with TEE.

Internal Medicine

Barssoum K, **Altibi AM**, Rai D, Kumar A, Kharsa A, Chowdhury M, Thakkar S, Shahid S, Abdelazeem M, Abuzaid AS, Baibhav B, Parikh V, Feitell SC, Balmer-Swain M, Rao M, Amsallem M, and Nanda NC. Speckle tracking echocardiography can predict subclinical myocardial involvement in patients with sarcoidosis: A meta-analysis. *Echocardiography* 2020; Epub ahead of print. PMID: 33058271. [Full Text](#)

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BACKGROUND: This meta-analysis aims to evaluate the utility of speckle tracking echocardiography (STE) as a tool to evaluate for cardiac sarcoidosis (CS) early in its course. Electrocardiography and echocardiography have limited sensitivity in this role, while advanced imaging modalities such as cardiac magnetic resonance (CMR) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) are limited by cost and availability. **METHODS:** We compiled English language articles that reported left ventricular global longitudinal strain (LVGLS) or global circumferential strain (GCS) in patients with confirmed extra-cardiac sarcoidosis versus healthy controls. Studies that exclusively included patients with probable or definite CS were excluded. Continuous data were pooled as a standard mean difference (SMD), comparing sarcoidosis group with healthy controls. A random-effect model was adopted in all analyses. Heterogeneity was assessed using Q and I² statistics. **RESULTS:** Nine studies were included in our final analysis with an aggregate of 967 patients. LVGLS was significantly lower in the extra-cardiac sarcoidosis group as compared with controls, SMD -3.98, 95% confidence interval (CI): -5.32, -2.64, P < .001, also was significantly lower in patients who suffered major cardiac events (MCE), -3.89, 95% CI -6.14, -1.64, P < .001. GCS was significantly lower in the extra-cardiac sarcoidosis group as compared with controls, SMD: -3.33, 95% CI -4.71, -1.95, P < .001. **CONCLUSION:** LVGLS and GCS were significantly lower in extra-cardiac sarcoidosis patients despite not exhibiting any cardiac symptoms. LVGLS correlates with MCEs in CS. Further studies are required to investigate the role of STE in the early screening of CS.

Internal Medicine

Gorgis S, Dabbagh MF, Mishra K, Ahluwalia G, Hana A, Fram G, Dhillon D, Lemor A, Khan A, Miller D, Kaatz S, O'Neill WW, and Wang DD. Unprotected discharge: absence of stroke prevention strategies in patients with atrial fibrillation admitted for bleeding. *J Interv Card Electrophysiol* 2020; Epub ahead of print. PMID: 33119818. [Full Text](#)

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PURPOSE: Patients with atrial fibrillation or flutter (AF) on anticoagulation (AC) for stroke prevention are at an increased risk of bleeding. A common clinical dilemma is deciding when to safely restart AC following a bleed. Although studies have shown better outcomes with re-initiation of AC after hemostasis, there are clinical barriers to restarting AC. Left atrial appendage occlusion (LAAO) is a safe and efficacious alternative for patients who are unable to tolerate AC following major bleeding. We aimed to evaluate the rate of stroke prevention strategies instituted at time of discharge in patients with AF on AC who had been hospitalized for a bleeding event. **METHODS:** We retrospectively identified patients with AF on AC admitted for bleeding between January 2016 and August 2019. The type of AC, form of bleeding, and CHA(2)DS(2)VASc were collected. Stroke prevention strategies upon discharge and at 3 months were noted. **RESULTS:** One hundred seventy-four patients with AF on AC were hospitalized with a bleeding event, of which 10.9% died. Among patients who survived, AC was restarted in 45.2% of patients, 9.7% were referred for LAAO, and 45.1% were discharged without stroke prevention strategy. At 3 months, 32.6% of patients still had no documented stroke prophylaxis. Those referred for LAAO had, on

average, higher CHA(2)DS(2)VASc (5 ± 1 vs 4 ± 1 , $p = 0.007$). CONCLUSIONS: A significant number of patients with AF hospitalized for bleeding were discharged with no plan for stroke prophylaxis. Despite its safety and efficacy, LAAO appears to be an underutilized alternative in AF patients with high bleeding risk.

Internal Medicine

Lanfeer DE, Luzum JA, She R, Gui H, Donahue MP, O'Connor CM, Adams KF, Sanders-van Wijk S, Zeld N, Maeder MT, Sabbah HN, Kraus WE, Brunner-La Rocca HP, Li J, and Williams LK. Polygenic Score for Beta-Blocker Survival Benefit in European Ancestry Patients with Reduced Ejection Fraction Heart Failure. *Circ Heart Fail* 2020; Epub ahead of print. PMID: 33012170. [Full Text](#)

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Background: Beta-blockers (BB) are mainstay therapy for heart failure with reduced ejection fraction (HFrEF). However, individual patient responses to BB vary, which may be partially due to genetic variation. The goal of this study was to derive and validate the first polygenic response predictor (PRP) for BB survival benefit in HFrEF patients. **Methods:** Derivation and validation analyses were performed in $n=1,436$ total HF patients of European descent and with $EF < 50\%$. The PRP was derived in a random subset of the Henry Ford Pharmacogenomic Registry (HFPGR; $n=248$), and then validated in a meta-analysis of the remaining patients from HFPGR ($n=247$), the TIME-CHF ($n=431$), and HF-ACTION trial ($n=510$). The PRP was constructed from a genome-wide analysis of BB*genotype interaction predicting time to all-cause mortality, adjusted for MAGGIC score, genotype, level of BB exposure, and BB propensity score. **Results:** Five-fold cross-validation summaries out to 1000 SNPs identified optimal prediction with a 44 SNP score and cutoff at the 30th percentile. In validation testing ($n=1188$) greater BB exposure was associated with reduced all-cause mortality in patients with low-PRP score ($n=251$; $HR=0.19$ [95% $CI=0.04-0.51$], $p=0.0075$), but not high-PRP score ($n=937$; $HR=0.84$ [95% $CI=0.53-1.3$], $p=0.448$), a difference that was statistically significant (p interaction = 0.0235). Results were consistent regardless of atrial fibrillation, EF ($\leq 40\%$ vs. $41-50\%$), or when examining cardiovascular death. **Conclusions:** Among patients of European ancestry with HFrEF, a PRP distinguished patients who derived substantial survival benefit from BB exposure from a larger group that did not. Additional work is needed prospectively test clinical utility and to develop PRPs for other population groups and other medications.

Internal Medicine

Liaqat H, Shirvanian N, Ammad Ud Din M, and Amin A. Cocaine-related vasculitis. *Clinical Case Reports* 2020; Epub ahead of print. PMID: Not assigned. [Full Text](#)

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Patients presenting with pancytopenia and a painful purpuric rash should be evaluated for levamisole-induced vasculitis and counseled about cocaine cessation as continued exposure can lead to permanent deformity of the involved areas.

Internal Medicine

Wang L, Pezeshkian K, Rayamajhi S, Herzallah K, Al-Abcha A, Olomu A, Kelly-Blake K, Yu E, and Wang DH. Relationship between blood pressure and kidney diseases in large randomized controlled trials: secondary analyses using SPRINT and ACCORD-BP trials. *J Hum Hypertens* 2020; Epub ahead of print. PMID: 33093616. [Full Text](#)

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Hypertension is a risk factor for acute kidney injury. In this study, we aimed to identify the optimal blood pressure (BP) targets for CKD and non-CKD patients. We analyzed the data of the Systolic Blood Pressure Intervention Trial (SPRINT) and the Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial (ACCORD BP) to determine the nonlinear relationship between BP and renal disease development using the Generalized Additive Model (GAM). Optimal systolic BP/diastolic BP (SBP/DBP) with lowest renal risk were estimated using GAM. Logistic regression was employed to find odds ratios (ORs) of adverse renal outcomes by three BP groups (high/medium/low). Both study trials have demonstrated a "U"-shaped relationship between BP and renal outcomes. For non-CKD patients in SPRINT trial, risk of 30% reduction in eGFR among intensive group patients with DBP \leq 70 mmHg was significantly higher than the group with DBP between 71 and 85 mmHg (OR = 2.31, 95% CI = 1.51-3.53). For non-CKD patients in ACCORD trial, risk of doubling of serum creatinine (SCr) or $>$ 20 mL/min decrease in eGFR among intensive group patients with DBP \leq 70 mmHg was significantly higher than the group with DBP between 71 and 85 mmHg (OR = 1.49, 95% CI = 1.12-1.99). For CKD patients in SPRINT trial, there are no significant differences in renal outcomes by different SBP/DBP levels. Our analysis of both SPRINT and ACCORD datasets demonstrated that lower-than-optimal DBP may lead to poor renal outcomes in non-CKD patients. Healthcare providers should be cautious of too low DBP level in intensive BP management due to poor renal outcomes for non-CKD patients.

Nephrology

Drawz PE, Agarwal A, Dwyer JP, Horwitz E, Lash J, Lenoir K, McWilliams A, Oparil S, Rahbari-Oskoui F, Rahman M, Parkulo MA, Pemu P, Raj DS, Rocco M, **Soman S**, Thomas G, Tuot DS, Whelton PK, and Pajewski NM. Concordance Between Blood Pressure in the Systolic Blood Pressure Intervention Trial and in Routine Clinical Practice. *JAMA Intern Med* 2020; Epub ahead of print. PMID: 33044494. [Full Text](#)

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IMPORTANCE: There are concerns with translating results from the Systolic Blood Pressure Intervention Trial (SPRINT) into clinical practice because the standardized protocol used to measure blood pressure (BP) may not be consistently applied in routine clinical practice. **OBJECTIVES:** To evaluate the concordance between BPs obtained in routine clinical practice and those obtained using the SPRINT protocol and whether concordance varied by target trial BP. **DESIGN, SETTING, AND PARTICIPANTS:** This observational prognostic study linking outpatient vital sign information from electronic health records (EHRs) with data from 49 of the 102 SPRINT sites was conducted from November 8, 2010, to August 20, 2015, among 3074 adults 50 years or older with hypertension without diabetes or a history of stroke. Statistical analysis was performed from May 21, 2019, to March 20, 2020. **MAIN OUTCOMES AND MEASURES:** Blood pressures measured in routine clinical practice and SPRINT. **RESULTS:** Participant-level EHR data was obtained for 3074 participants (2482 men [80.7%]; mean [SD] age, 68.5 [9.1] years) with 3 or more outpatient and trial BP measurements. In the period from the 6-month study visit to the end of the study intervention, the mean systolic BP (SBP) in the intensive treatment group from outpatient BP recorded in the EHR was 7.3 mm Hg higher (95% CI, 7.0-7.6 mm Hg) than BP measured at trial visits; the mean difference between BP recorded in the outpatient EHR and trial SBP was smaller for participants in the standard treatment group (4.6 mm Hg [95% CI, 4.4-4.9 mm Hg]). Bland-Altman analyses demonstrated low agreement between outpatient BP recorded in the EHR and trial BP, with wide agreement intervals ranging from approximately -30 mm Hg to 45 mm Hg in both treatment groups. In addition, the difference between BP recorded in the EHR and trial BP varied widely by site. **CONCLUSIONS AND RELEVANCE:** Outpatient BPs measured in routine clinical practice were generally higher than BP measurements taken in SPRINT, with greater mean SBP differences apparent in the intensive treatment group. There was a consistent high degree of heterogeneity between the BPs recorded in the EHR and trial BPs, with significant variability over time, between and within the participants, and across clinic sites. These results highlight the importance of proper BP measurement technique and an inability to apply 1 common correction factor (ie, approximately 10 mm Hg) to approximate research-quality BP estimates when BP is not measured appropriately in routine clinical practice. **TRIAL REGISTRATION:** SPRINT ClinicalTrials.gov Identifier: NCT01206062.

Nephrology

Shrivastava P, Prashar R, Khoury N, Patel A, Yeddula S, Kitajima T, Nagai S, and Samaniego M. Acute Kidney Injury in a Predominantly African American Cohort of Kidney Transplant Recipients With COVID-19 Infection. *Transplantation* 2020; Epub ahead of print. PMID: 33093403. [Full Text](#)

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Renal involvement in severe or critical acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is frequent. Acute kidney injury (AKI) in African American (AA) kidney transplant recipients (KTRs) with COVID-19 is not well described. We report our experience with a predominantly AA cohort (79%) of KTRs

with COVID-19 infections in the Detroit Metropolitan area. **METHODS:** In this retrospective, single-center study, we identified 39 KTRs who tested positive for SARS-CoV-2 between March 16 and April 25th, 2020. Data from electronic medical records were retrieved and compared between KTRs without AKI and KTRs with AKI. **RESULTS:** One pt was excluded due to DGF. Final analysis of AKI in KTRs with proven COVID-19 was done on 38 patients of which 30 were AA (79%). AKI occurred in 71.1% of COVID-19 KTRs (n=27), of whom 6 (22.2%) patients required HD. The incidence of AKI in our cohort was 71% (27/38). AKI rate among AA was 76.7% vs. 50% in non-AA cohort (p=0.195). In a univariate logistic regression analysis, AA race was not significantly associated with AKI OR (3.4, CI [0.68-17.4], p=0.14). After risk adjustment by race, patients with diabetes showed a significantly higher risk of AKI (adjusted OR 19.85 CI [1.65-58.66], p=0.012). KTRs with AKI had more preexisting RAAS inhibitor use than KTRs without AKI (P=0.03). **CONCLUSIONS:** KTRs infected with SARS-CoV-2 have a high incidence of AKI, with associated increased morbidity and mortality. Though no racial differences in mortality were noted in our KTRs with AKI, we await data from registries to help elucidate this difference.

Neurology

Frisoli TM, So CY, Guruswamy JG, Chebl AB, Lee JC, and Eng MH. Vacuuming in Crowded Dangerous Spaces: Aspiration of Large Ascending Aortic Thrombus. *JACC: Case Reports* 2020; 2(12):1979-1983. PMID: Not assigned. [Full Text](#)

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A patient had a stroke caused by a large, pedunculated aortic ascending mass and was deemed at high risk for near-term recurrent stroke. This case illustrates percutaneous aspiration thrombectomy of ascending aortic thrombus with the AngioVac system (Angiodynamics, Latham, New York), with conscious sedation for early stroke detection and with endovascular cerebral embolic protection. (Level of Difficulty: Intermediate.)

Neurology

Gilbert MR, Yuan Y, Wu J, Mendoza T, Vera E, Omuro A, Lieberman F, Robins HI, Gerstner ER, Wu J, Wen PY, **Mikkelsen T**, Aldape K, and Armstrong TS. A Phase II Study of Dose-Dense Temozolomide and Lapatinib for Recurrent Low-Grade and Anaplastic Supratentorial, Infratentorial, and Spinal Cord Ependymoma. *Neuro Oncol* 2020; Epub ahead of print. PMID: 33085768. [Full Text](#)

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BACKGROUND: No standard medical treatment exists for adult patients with recurrent ependymoma and prospective clinical trials in this population have not succeeded because of its rarity and challenges in accruing patients. The Collaborative Ependymoma Research Network (CERN) conducted a prospective phase II clinical trial of dose-dense temozolomide and lapatinib, targeting the unmethylated MGMT promoter status and increased expression of ErbB2 (HER2) and ErbB1 (EGFR) in ependymomas. **METHODS:** Patients age 18 or older with histologically proven and progressive ependymoma or anaplastic ependymoma were eligible and received dose-dense temozolomide and daily lapatinib. The primary outcome measure was median progression-free survival (PFS). Landmark 6- and 12-month PFS and objective response were measured. Serial assessments of symptom burden using the MDASI-BT/MDASI-SP were collected. **RESULTS:** The 50 patients enrolled had a median age of 43.5 years, median Karnofsky Performance Status of 90, and a median of 2 prior relapses. Twenty patients had grade III, 16 grade II, and 8 grade I ependymoma. Half had spinal cord tumors; 15 had a supratentorial tumor, 8 infratentorial, and 2 had disseminated disease. Treatment was well tolerated. The median PFS

was 7.8 months (95% CI 5.5,12.2); the 6-and 12-month PFS rates were 55% and 38%; with 2 complete and 6 partial responses. Measures of symptom burden showed reduction in moderate-severe pain and other disease-related symptoms in most patients. **CONCLUSIONS:** This treatment, with demonstrated clinical activity with objective responses and prolonged disease control associated with disease-related symptom improvements is an option as a salvage regimen for adult patients with recurrent ependymoma.

Neurology

Gorgis S, Dabbagh MF, Mishra K, Ahluwalia G, Hana A, Fram G, Dhillon D, Lemor A, Khan A, Miller D, Kaatz S, O'Neill WW, and Wang DD. Unprotected discharge: absence of stroke prevention strategies in patients with atrial fibrillation admitted for bleeding. *J Interv Card Electrophysiol* 2020; Epub ahead of print. PMID: 33119818. [Full Text](#)

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PURPOSE: Patients with atrial fibrillation or flutter (AF) on anticoagulation (AC) for stroke prevention are at an increased risk of bleeding. A common clinical dilemma is deciding when to safely restart AC following a bleed. Although studies have shown better outcomes with re-initiation of AC after hemostasis, there are clinical barriers to restarting AC. Left atrial appendage occlusion (LAAO) is a safe and efficacious alternative for patients who are unable to tolerate AC following major bleeding. We aimed to evaluate the rate of stroke prevention strategies instituted at time of discharge in patients with AF on AC who had been hospitalized for a bleeding event. **METHODS:** We retrospectively identified patients with AF on AC admitted for bleeding between January 2016 and August 2019. The type of AC, form of bleeding, and CHA(2)DS(2)VASc were collected. Stroke prevention strategies upon discharge and at 3 months were noted. **RESULTS:** One hundred seventy-four patients with AF on AC were hospitalized with a bleeding event, of which 10.9% died. Among patients who survived, AC was restarted in 45.2% of patients, 9.7% were referred for LAAO, and 45.1% were discharged without stroke prevention strategy. At 3 months, 32.6% of patients still had no documented stroke prophylaxis. Those referred for LAAO had, on average, higher CHA(2)DS(2)VASc (5 ± 1 vs 4 ± 1 , $p = 0.007$). **CONCLUSIONS:** A significant number of patients with AF hospitalized for bleeding were discharged with no plan for stroke prophylaxis. Despite its safety and efficacy, LAAO appears to be an underutilized alternative in AF patients with high bleeding risk.

Neurology

Popugaev KA, Bakharev SA, Kiselev KV, Samoylov AS, Samoylov NM, Abudeev SA, Zhuravel SV, Shabanov AK, Mueller T, **Mayer SA**, and Petrikov SS. Clinical and pathophysiological aspects of ECMO-associated hemorrhagic complications. *PLoS One* 2020; 15(10). PMID: 33048966. [Full Text](#)

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Extracorporeal membrane oxygenation (ECMO) is increasingly used to treat severe cases of acute respiratory or cardiac failure. Hemorrhagic complications represent one of the most common complications during ECMO, and can be life threatening. The purpose of this study was to elucidate pathophysiological mechanisms of ECMO-associated hemorrhagic complications and their impact on standard and viscoelastic coagulation tests. The study cohort included 27 patients treated with VV-ECMO or VA-ECMO. Hemostasis was evaluated using standard coagulation tests and viscoelastic parameters

investigated with rotational thromboelastometry. Anticoagulation and hemorrhagic complications were analyzed for up to seven days depending on ECMO duration. Hemorrhagic complications developed in 16 (59%) patients. There were 102 discrete hemorrhagic episodes among 116 24-hour-intervals, of which 27% were considered to be clinically significant. The highest number of ECMO-associated hemorrhages occurred on the 2nd and 3rd day of treatment. Respiratory tract bleeding was the most common hemorrhagic complication, occurring in 62% of the 24-hour intervals. All 24-hours-intervals were divided into two groups: "with bleeding" and "without bleeding". The probability of hemorrhage was significantly associated with abnormalities of four parameters: increased international normalized ratio (INR, sensitivity 71%, specificity 94%), increased prothrombin time (PT, sensitivity 90%, specificity 72%), decreased intrinsic pathway maximal clot firmness (MCFin, sensitivity 76%, specificity 89%), and increased extrinsic pathway clot formation time (CFTex, sensitivity 77%, specificity 87%). In conclusions, early ECMO-associated hemorrhagic complications are related to one traditional and two novel viscoelastic coagulation abnormalities: PT/INR elevation, reduced maximum clot firmness due to intrinsic pathway dysfunction (MCFin), and prolonged clot formation time due to extrinsic pathway dysfunction (CFTex). When managing hemostasis during ECMO, derangements in PT/INR, MCFin and CFTex should be focused on.

Neurology

Rodgers SA, Suneja A, Yoshida A, Abouljoud MS, and Otrrock ZK. Paradoxical embolic strokes in a liver transplant recipient with atrial septal defect undergoing therapeutic plasma exchange. *J Clin Apher* 2020; Epub ahead of print. PMID: 33058311. [Full Text](#)

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Therapeutic plasma exchange (TPE) is a technique used to separate blood components into layers based on their density difference, thus removing plasma and exchanging it with replacement fluids. A variety of adverse reactions has been described during TPE. Thrombotic events, especially strokes, are extremely rare complications of TPE. Our patient was a 55-year-old female with history of decompensated nonalcoholic steatohepatitis (NASH) liver cirrhosis. She underwent an orthotopic liver transplant (OLT) that was complicated with asystole during reperfusion. Cardiac workup revealed a new atrial septal defect (ASD) with left to right flow. Within the first 5 days after surgery, she developed refractory and persistent hyperbilirubinemia, with total bilirubin levels as high as 42 mg/dL. Our plasmapheresis service was consulted to initiate TPE. Towards the end of the first and only session of TPE, the patient developed hypoxia and left-sided hemiplegia. Stroke response was initiated, and the patient was intubated. MRI done 24 hours after the incident showed multiple acute small embolic infarcts scattered within the bilateral cerebral and cerebellar hemispheres. Bilateral lower and upper extremities venous duplex studies were positive for acute left internal jugular (IJ) vein thrombosis. Patient was treated with anticoagulation and the IJ catheter was removed. Patient also had closure of her ASD. On last follow up, she was doing well with complete reversal of neurologic deficits and stable liver function. Our patient had an uncommon complication of TPE. Her thrombosis manifested with multiple embolic strokes that would not have happened without an ASD with left to right flow.

Neurology

Shaikh AG, Beylergil SB, Scorr L, Kilic-Berkmen G, Freeman A, Klein C, Junker J, Loens S, Brüggemann N, Münchau A, Bäumer T, Vidailhet M, Roze E, Bonnet C, Jankovic J, Jimenez-Shahed J, **Patel N**, Marsh L, Comella C, Barbano RL, Berman BD, Malaty I, Shukla AW, Reich SG, Ledoux MS, Berardelli A, Ferrazzano G, Stover N, Ondo W, Richardson SP, Saunders-Pullman R, Mari Z, Agarwal P, Adler C, Chouinard S, Fox SH, Brashear A, Truong D, Suchowersky O, Frank S, Factor S, Perlmutter J, and Jinnah HA. Dystonia & tremor: A cross-sectional study of the dystonia coalition cohort. *Neurology* 2020; Epub ahead of print. PMID: 33046615. [Full Text](#)

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OBJECTIVE: To assess the clinical manifestations and predictors of different types of tremors in a individuals with different types of isolated dystonia. **METHODS:** Clinical manifestations of tremor were assessed in a multicenter, international cross-sectional, cohort study of 2362 individuals with all types of isolated dystonia (focal, segmental, multifocal and generalized) recruited through the Dystonia Coalition. **RESULTS:** Methodical and standardized assessments of all subjects in this cohort revealed the overall prevalence of any type of tremor was 53.3%. The prevalence of dystonic tremor varied from 36.9-48.4%, depending on criteria used to define it. To identify the factors associated with tremors in dystonia, the data were analyzed by generalized linear modeling and cluster analyses. Generalized linear modeling indicated two of the strongest factors associated with tremor included body region affected by dystonia and recruitment center. Tremor was also associated with severity of dystonia and duration of dystonia, but not with sex or race. The cluster analysis distinguished eight subgroups within the whole cohort; defined largely by body region affected with dystonia, and secondarily by other clinical characteristics. **CONCLUSION:** The large number of cases evaluated by an international team of movement disorder experts facilitated the dissection of several important factors that influence the apparent prevalence and

phenomenology of tremor in dystonia. These results are valuable for understanding the many differences reported in prior studies, and for guiding future studies of the nosology of tremor and dystonia.

Neurosurgery

Afzal M, Alam F, Malik KM, and **Malik GM**. Clinical Context-Aware Biomedical Text Summarization Using Deep Neural Network: Model Development and Validation. *J Med Internet Res* 2020; 22(10). PMID: 33095174. [Full Text](#)

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BACKGROUND: Automatic text summarization (ATS) enables users to retrieve meaningful evidence from big data of biomedical repositories to make complex clinical decisions. Deep neural and recurrent networks outperform traditional machine-learning techniques in areas of natural language processing and computer vision; however, they are yet to be explored in the ATS domain, particularly for medical text summarization. **OBJECTIVE:** Traditional approaches in ATS for biomedical text suffer from fundamental issues such as an inability to capture clinical context, quality of evidence, and purpose-driven selection of passages for the summary. We aimed to circumvent these limitations through achieving precise, succinct, and coherent information extraction from credible published biomedical resources, and to construct a simplified summary containing the most informative content that can offer a review particular to clinical needs. **METHODS:** In our proposed approach, we introduce a novel framework, termed Biomed-Summarizer, that provides quality-aware Patient/Problem, Intervention, Comparison, and Outcome (PICO)-based intelligent and context-enabled summarization of biomedical text. Biomed-Summarizer integrates the prognosis quality recognition model with a clinical context-aware model to locate text sequences in the body of a biomedical article for use in the final summary. First, we developed a deep neural network binary classifier for quality recognition to acquire scientifically sound studies and filter out others. Second, we developed a bidirectional long-short term memory recurrent neural network as a clinical context-aware classifier, which was trained on semantically enriched features generated using a word-embedding tokenizer for identification of meaningful sentences representing PICO text sequences. Third, we calculated the similarity between query and PICO text sequences using Jaccard similarity with semantic enrichments, where the semantic enrichments are obtained using medical ontologies. Last, we generated a representative summary from the high-scoring PICO sequences aggregated by study type, publication credibility, and freshness score. **RESULTS:** Evaluation of the prognosis quality recognition model using a large dataset of biomedical literature related to intracranial aneurysm showed an accuracy of 95.41% (2562/2686) in terms of recognizing quality articles. The clinical context-aware multiclass classifier outperformed the traditional machine-learning algorithms, including support vector machine, gradient boosted tree, linear regression, K-nearest neighbor, and naïve Bayes, by achieving 93% (16127/17341) accuracy for classifying five categories: aim, population, intervention, results, and outcome. The semantic similarity algorithm achieved a significant Pearson correlation coefficient of 0.61 (0-1 scale) on a well-known BIOSSES dataset (with 100 pair sentences) after semantic enrichment, representing an improvement of 8.9% over baseline Jaccard similarity. Finally, we found a highly positive correlation among the evaluations performed by three domain experts concerning different metrics, suggesting that the automated summarization is satisfactory. **CONCLUSIONS:** By employing the proposed method Biomed-Summarizer, high accuracy in ATS was achieved, enabling seamless curation of research evidence from the biomedical literature to use for clinical decision-making.

Neurosurgery

Ashraf O, Arzumanov G, Luther E, McMahon JT, Malcolm JG, Mansour S, **Lee IY**, Willie JT, Komotar RJ, and Danish SF. Magnetic resonance-guided laser interstitial thermal therapy for posterior fossa neoplasms. *J Neurooncol* 2020; Epub ahead of print. PMID: 33057919. [Full Text](#)

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PURPOSE: Magnetic resonance-guided laser interstitial thermal therapy (LITT) has been increasingly used to treat a number of intracranial pathologies, though its use in the posterior fossa has been limited to a few small series. We performed a multi-institutional review of targets in the posterior fossa, reporting the efficacy and safety profile associated with laser ablation in this region of the brain. **METHODS:** A retrospective review of patients undergoing LITT in the posterior fossa was performed from August 2010 to March 2020. Patient demographic information was collected alongside the operative parameters and patient outcomes. Reported outcomes included local control of the lesion, postoperative complications, hospital length of stay, and steroid requirements. **RESULTS:** 58 patients across four institutions underwent LITT in the posterior fossa for 60 tumors. The median pre-ablation tumor volume was 2.24 cm³. 48 patients (50 tumors) were available for follow-up. An 84% (42/50) overall local control rate was achieved at 9.5 months median follow up. There were two procedural complications, including insertional hemorrhage and laser misplacement and 12/58 (21%) patients developed new neurological deficits. There was one procedure related death. The median length of hospital stay was 1 day, with 20.7% of patients requiring discharge to a rehabilitation facility. **CONCLUSIONS:** LITT is an effective approach for treating pathology in the posterior fossa. The average target size is smaller than what has been reported in the supratentorial space. Care must be taken to prevent injury to surrounding structures given the close proximity of critical structures in this region.

Neurosurgery

Bier A, **Hong X**, **Czacu S**, Goldstein H, Rand D, **Xiang C**, **Jiang W**, Ben-Asher HW, **Attia M**, Brodie A, **She R**, **Poisson LM**, and Brodie C. miR-504 modulates the stemness and mesenchymal transition of glioma stem cells and their interaction with microglia via delivery by extracellular vesicles. *Cell Death Dis* 2020; 11(10):899. PMID: 33093452. [Full Text](#)

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Glioblastoma (GBM) is a highly aggressive tumor with poor prognosis. A small subpopulation of glioma stem cells (GSCs) has been implicated in radiation resistance and tumor recurrence. In this study we analyzed the expression of miRNAs associated with the functions of GSCs using miRNA microarray analysis of these cells compared with human neural stem cells. These analyses identified gene clusters associated with glioma cell invasiveness, axonal guidance, and TGF- β signaling. miR-504 was significantly downregulated in GSCs compared with NSCs, its expression was lower in GBM compared with normal brain specimens and further decreased in the mesenchymal glioma subtype. Overexpression of miR-504 in GSCs inhibited their self-renewal, migration and the expression of mesenchymal markers. The inhibitory effect of miR-504 was mediated by targeting Grb10 expression which acts as an oncogene in GSCs and GBM. Overexpression of exogenous miR-504 resulted also in its delivery to cocultured microglia by GSC-secreted extracellular vesicles (EVs) and in the abrogation of the GSC-induced polarization of microglia to M2 subtype. Finally, miR-504 overexpression prolonged the survival of mice harboring GSC-derived xenografts and decreased tumor growth. In summary, we identified miRNAs and potential target networks that play a role in the stemness and mesenchymal transition of GSCs and the

miR-504/Grb10 pathway as an important regulator of this process. Overexpression of miR-504 exerted antitumor effects in GSCs as well as bystander effects on the polarization of microglia via delivery by EVs.

Neurosurgery

Chaudhry F, Hunt RJ, Hariharan P, Anand SK, Sanjay S, Kjoller EE, Bartlett CM, Johnson KW, Levy PD, Noushmehr H, and Lee IY. Machine Learning Applications in the Neuro ICU: A Solution to Big Data Mayhem? *Frontiers in Neurology* 2020; 11. PMID: Not assigned. [Full Text](#)

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The neurological ICU (neuro ICU) often suffers from significant limitations due to scarce resource availability for their neurocritical care patients. Neuro ICU patients require frequent neurological evaluations, continuous monitoring of various physiological parameters, frequent imaging, and routine lab testing. This amasses large amounts of data specific to each patient. Neuro ICU teams are often overburdened by the resulting complexity of data for each patient. Machine Learning algorithms (ML), are uniquely capable of interpreting high-dimensional datasets that are too difficult for humans to comprehend. Therefore, the application of ML in the neuro ICU could alleviate the burden of analyzing big datasets for each patient. This review serves to (1) briefly summarize ML and compare the different types of MLs, (2) review recent ML applications to improve neuro ICU management and (3) describe the future implications of ML to neuro ICU management.

Neurosurgery

Cloughesy TF, Petrecca K, **Walbert T**, Butowski N, Salacz M, Perry J, Damek D, Bota D, Bettegowda C, Zhu JJ, Iwamoto F, Placantonakis D, Kim L, Elder B, Kaptain G, Cachia D, Moshel Y, Brem S, Piccioni D, Landolfi J, Chen CC, Gruber H, Rao A, Hogan D, Accomando W, Ostertag D, Montellano TT, Kheoh T, Kabbinnavar F, and Vogelbaum MA. Effect of Vocimagene Amiretrorepevec in Combination With Flucytosine vs Standard of Care on Survival Following Tumor Resection in Patients With Recurrent High-Grade Glioma: A Randomized Clinical Trial. *JAMA Oncol* 2020; Epub ahead of print. PMID: 33119048.

[Full Text](#)

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Impossible Foods, San Francisco, California.
Fate Therapeutics, San Diego, California.
Abintus Bio, San Diego, California.
Kura Oncology, San Diego, California.
Mirati Therapeutics, San Diego, California.
Puma Biotechnology, Los Angeles, California.
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IMPORTANCE: New treatments are needed to improve the prognosis of patients with recurrent high-grade glioma. **OBJECTIVE:** To compare overall survival for patients receiving tumor resection followed by vocimagene amiretrorepvec (Toca 511) with flucytosine (Toca FC) vs standard of care (SOC). **DESIGN, SETTING, AND PARTICIPANTS:** A randomized, open-label phase 2/3 trial (TOCA 5) in 58 centers in the US, Canada, Israel, and South Korea, comparing posttumor resection treatment with Toca 511 followed by Toca FC vs a defined single choice of approved (SOC) therapies was conducted from November 30, 2015, to December 20, 2019. Patients received tumor resection for first or second recurrence of glioblastoma or anaplastic astrocytoma. **INTERVENTIONS:** Patients were randomized 1:1 to receive Toca 511/FC (n = 201) or SOC control (n = 202). For the Toca 511/FC group, patients received Toca 511 injected into the resection cavity wall at the time of surgery, followed by cycles of oral Toca FC 6 weeks after surgery. For the SOC control group, patients received investigators' choice of single therapy: lomustine, temozolomide, or bevacizumab. **MAIN OUTCOMES AND MEASURES:** The primary outcome was overall survival (OS) in time from randomization date to death due to any cause. Secondary outcomes reported in this study included safety, durable response rate (DRR), duration of DRR, durable clinical benefit rate, OS and DRR by IDH1 variant status, and 12-month OS. **RESULTS:** All 403 randomized patients (median [SD] age: 56 [11.46] years; 62.5% [252] men) were included in the efficacy analysis, and 400 patients were included in the safety analysis (3 patients on the SOC group did not receive resection). Final analysis included 271 deaths (141 deaths in the Toca 511/FC group and 130 deaths in the SOC control group). The median follow-up was 22.8 months. The median OS was 11.10 months for the Toca 511/FC group and 12.22 months for the control group (hazard ratio, 1.06; 95% CI 0.83, 1.35; P = .62). The secondary end points did not demonstrate statistically significant differences. The rates of adverse events were similar in the Toca 511/FC group and the SOC control group. **CONCLUSIONS AND RELEVANCE:** Among patients who underwent tumor resection for first or second recurrence of glioblastoma or anaplastic astrocytoma, administration of Toca 511 and Toca FC, compared with SOC, did not improve overall survival or other efficacy end points. **TRIAL REGISTRATION:** ClinicalTrials.gov Identifier: NCT02414165.

Neurosurgery

Golebiewska A, Hau AC, Oudin A, Stieber D, Yabo YA, Baus V, Barthelemy V, Klein E, Bougnaud S, Keunen O, Wantz M, Michelucci A, Neirinckx V, Muller A, Kaoma T, Nazarov PV, Azuaje F, De Falco A, Flies B, Richart L, Poovathingal S, Arns T, Grzyb K, Mock A, Herold-Mende C, Steino A, Brown D, May P, Miletic H, **Malta TM**, **Noushmehr H**, Kwon YJ, Jahn W, Klink B, Tanner G, Stead LF, Mittelbronn M, Skupin A, Hertel F, Bjerkvig R, and Niclou SP. Patient-derived organoids and orthotopic xenografts of primary and recurrent gliomas represent relevant patient avatars for precision oncology. *Acta Neuropathol* 2020; Epub ahead of print. PMID: 33009951. [Full Text](#)

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Patient-based cancer models are essential tools for studying tumor biology and for the assessment of drug responses in a translational context. We report the establishment a large cohort of unique organoids and patient-derived orthotopic xenografts (PDOX) of various glioma subtypes, including gliomas with mutations in IDH1, and paired longitudinal PDOX from primary and recurrent tumors of the same patient. We show that glioma PDOXs enable long-term propagation of patient tumors and represent clinically relevant patient avatars that retain histopathological, genetic, epigenetic, and transcriptomic features of parental tumors. We find no evidence of mouse-specific clonal evolution in glioma PDOXs. Our cohort captures individual molecular genotypes for precision medicine including mutations in IDH1, ATRX, TP53, MDM2/4, amplification of EGFR, PDGFRA, MET, CDK4/6, MDM2/4, and deletion of CDKN2A/B, PTCH, and PTEN. Matched longitudinal PDOX recapitulate the limited genetic evolution of gliomas observed in patients following treatment. At the histological level, we observe increased vascularization in the rat host as compared to mice. PDOX-derived standardized glioma organoids are amenable to high-throughput drug screens that can be validated in mice. We show clinically relevant responses to temozolomide (TMZ) and to targeted treatments, such as EGFR and CDK4/6 inhibitors in (epi)genetically defined subgroups, according to MGMT promoter and EGFR/CDK status, respectively. Dianhydrogalactitol (VAL-083), a promising bifunctional alkylating agent in the current clinical trial, displayed high therapeutic efficacy, and was able to overcome TMZ resistance in glioblastoma. Our work underscores the clinical relevance of glioma organoids and PDOX models for translational research and personalized treatment studies and represents a unique publicly available resource for precision oncology.

Neurosurgery

Malik KM, Krishnamurthy M, Alam F, **Zakaria H**, and **Malik G**. Introducing the Rupture Criticality Index to Compare Risk Factor Combinations Associated with Aneurysmal Rupture. *World Neurosurg* 2020; Epub ahead of print. PMID: 33045451. [Full Text](#)

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BACKGROUND: Relative risk is insufficient to guide treatment decision making for unruptured intracranial aneurysms. **OBJECTIVE:** To introduce a novel risk assessment methodology called Rupture Criticality Index (RCI), which allows for concurrent evaluation of groups of risk factors (RFs). **METHODS:** From a retrospective database of saccular aneurysms, we identify 915 patients and delineate 50 potential RFs for aneurysms in 11 unique locations. RF combinations for multivariable analysis were defined by aneurysm

size, location, and a third variable from the study design. Data analysis was performed by applying frequency distribution methods to define the RCI of each RF combination. RESULTS: RF combinations at greatest risk were small (4.8-8.2 mm) or medium (8.3-14.5 mm) anterior communicating aneurysms (ACoA) in males (RCI 9.87-10), small ACoA in ≤ 37 years or 38-55 years (RCI 8.67-8.99), medium basilar tip aneurysms (BTA) in males (RCI 10), and large (14.6-22.5 mm) BTA in Caucasians or 38-55 years (RCI 9.25 & 9.35). CONCLUSION: We introduce the concept of RCI and compare how RF combinations are associated with aneurysmal rupture. This novel approach to aneurysmal rupture identifies high-risk clinical presentations and can be used to guide clinical decision making in patients with non-traditional risks.

Neurosurgery

Muralidharan K, Yekula A, Small JL, Rosh ZS, Kang KM, Wang L, Lau S, Zheng H, Lee H, Bettegowda C, Chicoine MR, **Kalkanis S**, Shankar GM, Nahed BV, Curry WT, Jones PS, Cahill DP, Balaj L, and Carter BS. TERT promoter mutation analysis for blood-based diagnosis and monitoring of gliomas. *Clin Cancer Res* 2020; Epub ahead of print. PMID: 33051308. [Full Text](#)

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PURPOSE: Liquid biopsy offers a minimally invasive tool to diagnose and monitor the heterogeneous molecular landscape of tumors over time and therapy. Detection of TERT promoter mutations (C228T, C250T) in cfDNA has been successful for some systemic cancers but has yet to be demonstrated in gliomas, despite the high prevalence of these mutations in glioma tissue (>60% of all tumors).

EXPERIMENTAL DESIGN: Here, we developed a novel digital droplet PCR (ddPCR) assay, that incorporates features to improve sensitivity and allows for the simultaneous detection and longitudinal monitoring of two TERT promoter mutations (C228T and C250T) in cfDNA from the plasma of glioma patients. RESULTS: In baseline performance in tumor tissue, the assay had perfect concordance with an independently performed clinical pathology laboratory assessment of TERT promoter mutations in the same tumor samples (95% CI 94%-100%). Extending to matched plasma samples, we detected TERT mutations in both discovery and blinded multi-institution validation cohorts with an overall sensitivity of 62.5% (95% CI 52%-73%) and a specificity of 90% (95% CI 80%-96%) compared to the gold standard tumor tissue-based detection of TERT mutations. Upon longitudinal monitoring in 5 patients, we report that peripheral TERT mutant allele frequency reflects the clinical course of the disease with levels decreasing after surgical intervention and therapy and increasing with tumor progression.

CONCLUSIONS: Our results demonstrate the feasibility of detecting circulating cfDNA TERT promoter mutations in glioma patients with clinically relevant sensitivity and specificity.

Neurosurgery

Peereboom DM, Ye X, **Mikkelsen T**, Lesser GJ, Lieberman FS, Robins HI, Ahluwalia MS, Sloan AE, and Grossman SA. A Phase II and Pharmacodynamic Trial of RO4929097 for Patients With Recurrent/Progressive Glioblastoma. *Neurosurgery* 2020; Epub ahead of print. PMID: 33027815. [Full Text](#)

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BACKGROUND: Cancer stem-like cells are a major cause of resistance to therapy in patients with glioblastoma (GBM) as well as other cancers. Tumor cells are maintained in a stem-like proliferative state in large part through the Notch signaling pathway. The function of this pathway in turn depends on gamma secretase activity. Inhibition of this enzyme therefore inhibits the Notch pathway and tumor growth as measured by a reduction in the formation of brain tumor neurospheres in murine models. RO4929097 is an oral gamma secretase inhibitor. **OBJECTIVE:** To estimate the 6-mo progression-free survival rate (PFS6) in patients with progressive GBM and to inhibit by 50% the generation of neurospheres in fresh tissue resected from patients treated with RO4929097. **METHODS:** In this phase II and pharmacodynamic study, patients with recurrent GBM received RO4929097 in a study of 2 groups. Group A patients had unresectable disease and received drug in a standard phase II design. Group B patients had resectable disease and received drug before and after surgical resection. Endpoints included PFS6 and the inhibition of neurosphere formation in the resected tumor samples. **RESULTS:** A total of 47 patients received treatment, 7 of whom had tumor resection. The PFS6 was 4%, and the inhibition of neurosphere formation occurred in 1 of 7 patient samples. **CONCLUSION:** RO4929097 was inactive in recurrent GBM patients and demonstrated minimal inhibition of neurosphere formation in fresh tissue samples.

Neurosurgery

Wang MC, Boop FA, Kondziolka D, Resnick DK, **Kalkanis SN**, Koehnen E, Selden NR, Heilman CB, Valadka AB, Cockroft KM, Wilson JA, Ellenbogen RG, Asher AL, Byrne RW, Camarata PJ, Huang J, Knightly JJ, Levy EI, Lonser RR, Connolly ES, Meyer FB, and Liau LM. Continuous improvement in patient safety and quality in neurological surgery: the American Board of Neurological Surgery in the past, present, and future. *J Neurosurg* 2020; Epub ahead of print. PMID: 33065539. [Full Text](#)

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The American Board of Neurological Surgery (ABNS) was incorporated in 1940 in recognition of the need for detailed training in and special qualifications for the practice of neurological surgery and for self-regulation of quality and safety in the field. The ABNS believes it is the duty of neurosurgeons to place a patient's welfare and rights above all other considerations and to provide care with compassion, respect for human dignity, honesty, and integrity. At its inception, the ABNS was the 13th member board of the American Board of Medical Specialties (ABMS), which itself was founded in 1933. Today, the ABNS is one of the 24 member boards of the ABMS. To better serve public health and safety in a rapidly changing healthcare environment, the ABNS continues to evolve in order to elevate standards for the practice of neurological surgery. In connection with its activities, including initial certification, recognition of focused practice, and continuous certification, the ABNS actively seeks and incorporates input from the public and the physicians it serves. The ABNS board certification processes are designed to evaluate both real-life subspecialty neurosurgical practice and overall neurosurgical knowledge, since most neurosurgeons provide call coverage for hospitals and thus must be competent to care for the full spectrum of neurosurgery. The purpose of this report is to describe the history, current state, and anticipated future direction of ABNS certification in the US.

Nursing

Nemeh H, Coba V, Chulkov M, Gupta A, Yeldo N, Chamogeorgakis T, Tanaka D, Allenspach L, Simanovski J, and Shanti C. Lung Transplantation for the Treatment of Vaping Induced, Irreversible, End Stage Lung Injury. *Ann Thorac Surg* 2020; Epub ahead of print. PMID: 33130115. [Full Text](#)

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Recently, there has been a rise in the incidence of E-cigarettes/Vaping Associated Lung Injury (EVALI) in the United States mostly involving Tetrahydrocannabinol (THC)(1). Present treatment strategies for EVALI are aimed at controlling the inflammatory and infectious etiologies in addition to supportive care(2). While most patients improve with supportive measures(3,4) the long-term pulmonary effects of this illness are still not well defined. In this report, we describe a case of EVALI resulting in progressive, irreversible destruction of the lung parenchyma that was treated with double lung transplantation.

Nursing

Surabenjawong U, Phrampus PE, Lutz J, Farkas D, **Gopalakrishna A**, Monsomboon A, Limsuwat C, and O'Donnell JM. Comparison of Innovative Peer-to-Peer Education and Standard Instruction on Airway Management Skill Training. *Clinical Simulation in Nursing* 2020; 47:16-24. PMID: Not assigned. [Full Text](#)

Background: Innovative peer-to-peer teaching has the potential to emphasize student self-Learning and reduce the workload of the instructor. Method: This single-blinded randomized crossover trial was conducted to evaluate whether peer-to-peer teaching is not inferior to standard teaching in basic airway management for undergraduate nursing students. Results: Forty-eight students with the peer-to-peer Learning had significantly higher skill rating scores with a Large effect size (Cohen's d of 1.07 (p-value .002) for oropharyngeal airway insertion, 1.14 (p-value <.001) for nasopharyngeal airway insertion, and 0.81 (p-value .003) for bag-mask ventilation). There was no difference between preknowledge and postknowledge scores (p-value of .13 and .22, respectively). Both groups reported higher confidence. Conclusions: Nursing students trained in basic airway management by the peer-to-peer method did not show inferiority compared with the standard group. (C) 2020 International Nursing Association for Clinical Simulation and Learning. Published by Elsevier Inc. All rights reserved.

Obstetrics, Gynecology, and Women's Health

Zhu S, Khalil R, Altairy O, Burmeister C, Dimitrova I, and Elshaikh M. Increased risk of recurrence in early-stage endometrial carcinoma after delays in adjuvant radiation treatment. *Int J Gynecol Cancer* 2020; Epub ahead of print. PMID: 33087415. [Full Text](#)

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OBJECTIVE: The benefits of adjuvant radiation treatment after hysterectomy have been confirmed in select patients with early-stage endometrial carcinoma. The goal of this study was to evaluate the prognostic impact of the time interval between hysterectomy and starting adjuvant radiation treatment in patients with early-stage endometrial carcinoma. **METHODS:** Our database was searched for women with early-stage endometrioid endometrial cancer who received adjuvant radiation therapy after hysterectomy. The patients were classified into two groups based on the time interval to adjuvant radiation therapy (≤ 8 weeks or > 8 weeks) after hysterectomy. Recurrence-free survival, disease-specific survival, and overall survival were compared between the two groups. **RESULTS:** Four hundred and sixty patients were identified. Median follow-up was 70.5 months (range 1-360). One hundred and seventy-six patients (38%) were 2009 International Federation of Gynecology and Obstetrics stage IA, 207 (45%) stage IB, and 77 (17%) stage II. Three hundred and fifty-four women (77%) received adjuvant radiation therapy within 8 weeks after hysterectomy. There was no statistically significant difference between the two groups in baseline demographics, disease and treatment characteristics, except for the modality of adjuvant radiation therapy. Patients who received adjuvant radiation therapy within 8 weeks experienced significantly less disease recurrence (9% vs 18%; $p=0.01$) and particularly less isolated vaginal recurrence (0% vs 6%, $p=0.04$). Five-year recurrence-free survival was 89% versus 80% ($p=0.04$), 5-year disease-specific survival was 93% for both groups, and 5-year overall survival was 86% versus 85% for patients who received adjuvant radiation therapy ≤ 8 and > 8 weeks, respectively ($p=0.88$). **CONCLUSION:** Our study suggests that delaying adjuvant radiation therapy beyond 8 weeks after hysterectomy is associated with significantly more cancer recurrences for women with early-stage endometrial carcinoma.

Orthopaedics/Bone and Joint

Makhni EC. Meaningful Clinical Applications of Patient-Reported Outcome Measures in Orthopaedics. *J Bone Joint Surg Am* 2020; Epub ahead of print. PMID: 33079895. [Full Text](#)

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Orthopaedics/Bone and Joint

Oravec D, Zauel R, Flynn MJ, and Yeni YN. Vertebral stiffness measured via tomosynthesis-based digital volume correlation is strongly correlated with reference values from micro-CT-based DVC. *Med Eng Phys* 2020; 84:169-173. PMID: 32977915. [Full Text](#)

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Digital tomosynthesis (DTS) is a clinically available modality that allows imaging of a patient's spine in supine and standing positions. The purpose of this study was to establish the extent to which vertebral displacement and stiffness derived from DTS-based digital volume correlation (DTS-DVC) are correlated with those from a reference method, i.e., microcomputed tomography-based DVC (μ CT-DVC). T11 vertebral bodies from 11 cadaveric donors were DTS imaged twice in a nonloaded state and once under a fixed load level approximating upper body weight. The same vertebrae were μ CT imaged in nonloaded and loaded states (40 μ m voxel size). Vertebral displacements were calculated at each voxel using DVC

with pairs of nonloaded and loaded images, from which endplate-to-endplate axial displacement (D(DVC)) and vertebral stiffness (S(DVC)) were calculated. Both D(DVC) and S(DVC) demonstrated strong positive correlations between DTS-DVC and μ CT-DVC, with correlations being stronger when vertebral displacement was calculated using the median ($R(2)=0.80$; $p<0.0002$ and $R(2)=0.93$; $p<0.0001$, respectively) rather than average displacement ($R(2)=0.63$; $p<0.004$ and $R(2)=0.69$; $p<0.002$, respectively). In conclusion, the demonstrated relationship of DTS-DVC with the μ CT standard supports further development of a biomechanics-based clinical assessment of vertebral bone quality using the DTS-DVC technique.

Otolaryngology

Margalit DN, Sacco AG, Cooper JS, Ridge JA, Bakst RL, Beadle BM, Beitler JJ, **Chang SS**, Chen AM, Galloway TJ, Koyfman SA, Mita C, Robbins JR, Tsai CJ, Truong MT, Yom SS, and **Siddiqui F**. Systematic review of postoperative therapy for resected squamous cell carcinoma of the head and neck: Executive summary of the American Radium Society appropriate use criteria. *Head Neck* 2020; Epub ahead of print. PMID: 33098180. [Full Text](#)

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BACKGROUND: The aims of this systematic review are to (a) evaluate the current literature on the impact of postoperative therapy for resected squamous cell carcinoma of the head and neck (SCCHN) on oncologic and non-oncologic outcomes and (b) identify the optimal evidence-based postoperative therapy recommendations for commonly encountered clinical scenarios. **METHODS:** An analysis of the medical literature from peer-reviewed journals was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline. Prospective studies and methodology-based systematic reviews and meta-analyses of postoperative therapy for SCCHN were identified by searching Medline (OVID) and EMBASE (Elsevier) using controlled vocabulary terms (ie, National Library of Medicine Medical Subject Headings [MeSH], Emtree). Study screening and selection was performed with Covidence software and full-text review. The RAND/UCLA appropriateness method was used by the expert panel to rate the appropriate use of postoperative therapy, and the modified Delphi method was used to come to consensus. **RESULTS:** A total of 5660 studies were identified and screened using the title and abstract, leading to 201 studies assessed for relevance using full-text review. After limitation to the eligibility criteria, 101 studies from 1977 to 2020 were identified, including 77 with oncologic endpoints and 24 with function and quality of life endpoints. All studies reported staging prior to the implementation of American Joint Committee on Cancer (AJCC-8). **CONCLUSIONS:** Prospective clinical studies and systematic reviews identified through the PRISMA systematic review provided good evidence for consensus statements regarding the appropriate use of postoperative therapy for resected SCCHN. Further research is needed in domains where consensus by the expert panel could not be achieved for the appropriateness of specific postoperative therapeutic interventions.

Otolaryngology

Tsai CJ, Galloway TJ, Margalit DN, Bakst RL, Beadle BM, Beitler JJ, **Chang S**, Chen A, Cooper J, Koyfman SA, Ridge JA, Robbins J, Truong MT, Yom SS, and **Siddiqui F**. Ipsilateral radiation for squamous cell carcinoma of the tonsil: American Radium Society appropriate use criteria executive summary. *Head Neck* 2020; Epub ahead of print. PMID: 33068064. [Full Text](#)

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BACKGROUND: We conducted the current systemic review to provide up-to-date literature summary and optimal evidence-based recommendations for ipsilateral radiation for squamous cell carcinoma of the tonsil. **METHODS:** We performed literature search of peer-reviewed journals through PubMed. The search strategy and subject-specific keywords were developed based on the expert panel's consensus. Articles published from January 2000 to May 2020 with full text available on PubMed and restricted to the English language and human subjects were included. Several prespecified search terms were used to identify relevant publications and additional evidence published since the initial American College of Radiology Appropriateness Criteria Ipsilateral Tonsil Radiation recommendation was finalized in 2012. The full bibliographies of identified articles were reviewed and irrelevant studies were removed. **RESULTS:** The initial search and review returned 46 citations. The authors added three citations from bibliographies, websites, or books not found in the literature search. Of the 49 citations, 30 citations were retained for further detailed review, and 14 of them were added to the evidence table. Articles were removed from the bibliography if they were not relevant or generalizable to the topic, or focused on unknown primary disease. Several commonly encountered clinical case variants were created and panelists anonymously rated each treatment recommendation. The results were reviewed and disagreements discussed. **CONCLUSIONS:** The panel provided updated evidence and recommendations for ipsilateral radiation for squamous cell carcinoma of the tonsil in the setting of primary radiation-based therapy and postoperative adjuvant radiotherapy. This committee did not reach agreements for some case variants due to a lack of strong evidence supporting specific treatment decisions, indicating a further need for research in these topics.

Pathology

Baine MK, Hsieh MS, Lai WV, Egger JV, Jungbluth A, Daneshbod Y, Beras A, Spencer R, Lopardo J, Bodd F, **Montecalvo J**, Sauter JL, Chang JC, Buonocore DJ, Travis WD, Sen T, Poirier JT, Rudin CM, and Rekhman N. Small Cell Lung Carcinoma Subtypes Defined by ASCL1, NEUROD1, POU2F3 and YAP1: Comprehensive Immunohistochemical and Histopathologic Characterization. *J Thorac Oncol* 2020; Epub ahead of print. PMID: 33011388. [Request Article](#)

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INTRODUCTION: Recent studies have identified subtypes of small cell lung carcinoma (SCLC) defined by RNA expression of ASCL1, NEUROD1, POU2F3 and YAP1 transcriptional regulators. There are only limited data on distribution of these markers at the protein level and associated pathologic characteristics in clinical SCLC samples. **METHODS:** Expression of ASCL1, NEUROD1, POU2F3 and YAP1 was analyzed by immunohistochemistry in 174 SCLC patient samples. Subtypes defined by these markers were correlated with histologic characteristics, expression of neuroendocrine markers (synaptophysin, chromogranin A, CD56, INSM1) and other SCLC markers including neuroendocrine phenotype-associated marker DLL3. **RESULTS:** ASCL1 and NEUROD1 expression had the following distribution: ASCL1+/NEUROD1- 41%, ASCL1+/NEUROD1+ 37%, ASCL1-/NEUROD1+ 8% and ASCL1-/NEUROD1- 14%. Based on the relative expression, 69% of cases were ASCL1-dominant and 17% NEUROD1-dominant. POU2F3 was expressed in 7% of SCLC, and was mutually exclusive of ASCL1 and NEUROD1. YAP1 was expressed at low levels, primarily in combined SCLC, and was not exclusive of other subtypes. Both ASCL1-dominant and NEUROD1-dominant subtypes were associated with neuroendocrine marker(high)/DLL3(high) profile, whereas POU2F3 and other ASCL1/NEUROD1-double-negative tumors were neuroendocrine marker(low)/DLL3(low). **CONCLUSIONS:** This is the first comprehensive immunohistochemical and histopathologic analysis of novel SCLC subtypes in patient samples. We confirm that ASCL1/NEUROD1-double-negative tumors represent a distinct neuroendocrine-low subtype of SCLC which is either uniquely associated with POU2F3 or lacks a known dominant regulator. Expression profiles of these markers appear more heterogeneous in native samples than in experimental models, particularly in regard to high prevalence of ASCL1/NEUROD1 co-expression. These findings may have prognostic and therapeutic implications and warrant further clinical investigation.

Pathology

Filkins L, Hauser JR, Robinson-Dunn B, **Tibbetts R**, Boyanton BL, Jr., and Revell P. American Society for Microbiology provides 2020 Guidelines for Detection and Identification of Group B Streptococcus. *J Clin Microbiol* 2020; Epub ahead of print. PMID: 33115849. [Full Text](#)

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Maternal colonization with Group B Streptococcus (GBS) is a primary risk factor for early-onset disease (EOD) GBS infection in infants and intrapartum prophylaxis reduces neonatal infection.

Pathology

Omark J, Masunaga Y, Hannibal M, **Shaw B**, Fukami M, Kato F, Saitsu H, Kagami M, and Ogata T. Kagami-Ogata syndrome in a patient with 46,XX,t(2;14)(q11.2;q32.2)mat disrupting MEG3. *J Hum Genet* 2020; Epub ahead of print. PMID: 33067531. [Request Article](#)

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Kagami-Ogata syndrome (KOS14) is a rare imprinting disorder characterized by a unique constellation of phenotypes including bell-shaped small thorax with coat-hanger appearance of the ribs. We encountered an African American female infant with KOS14 phenotype and 46,XX,t(2;14)(q11.2;q32.2)mat. After excluding upd(14)pat and an epimutation (hypermethylation) and a deletion affecting the maternally derived 14q32.2 imprinted region, we performed whole-genome sequencing, revealing that the translocation was generated between noncoding region at 2q11.2 and intron 6 of MEG3 at 14q32.2. Subsequent Sanger sequencing for the fusion points showed that the chromosomal fusion on the der(2) chromosome occurred between Chr2:102,193,994 (bp) and Chr14:101,314,628 (bp) in association with an insertion of 5-bp segment of unknown origin and that on the der(14) chromosome took place between Chr14:101,314,627 (bp) and Chr2:102,193,995 (bp) in association with an insertion of 1-bp segment of unknown origin (according to GRCh37/hg19). The results, together with the previous data in patients with KOS14, imply that the MEG3 disruption by 46,XX,t(2;14)(q11.2;q32.2)mat caused silencing of all MEGs including RTL1as and resultant excessive RTL1 expression, leading to the development of KOS14. To our knowledge, while Robertsonian translocations involving chromosome 14 have been reported in KOS14, this is the first case of KOS14 caused by a chromosomal translocation involving the 14q32.2 imprinted region.

Pathology

Rodgers SA, Suneja A, Yoshida A, Abouljoud MS, and Otrrock ZK. Paradoxical embolic strokes in a liver transplant recipient with atrial septal defect undergoing therapeutic plasma exchange. *J Clin Apher* 2020; Epub ahead of print. PMID: 33058311. [Full Text](#)

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Therapeutic plasma exchange (TPE) is a technique used to separate blood components into layers based on their density difference, thus removing plasma and exchanging it with replacement fluids. A variety of adverse reactions has been described during TPE. Thrombotic events, especially strokes, are extremely rare complications of TPE. Our patient was a 55-year-old female with history of decompensated nonalcoholic steatohepatitis (NASH) liver cirrhosis. She underwent an orthotopic liver transplant (OLT) that was complicated with asystole during reperfusion. Cardiac workup revealed a new atrial septal defect (ASD) with left to right flow. Within the first 5 days after surgery, she developed refractory and persistent hyperbilirubinemia, with total bilirubin levels as high as 42 mg/dL. Our plasmapheresis service was consulted to initiate TPE. Towards the end of the first and only session of TPE, the patient developed hypoxia and left-sided hemiplegia. Stroke response was initiated, and the patient was intubated. MRI done 24 hours after the incident showed multiple acute small embolic infarcts scattered within the bilateral cerebral and cerebellar hemispheres. Bilateral lower and upper extremities venous duplex studies were positive for acute left internal jugular (IJ) vein thrombosis. Patient was treated with anticoagulation and the IJ catheter was removed. Patient also had closure of her ASD. On last follow up, she was doing well with complete reversal of neurologic deficits and stable liver function. Our patient had an uncommon complication of TPE. Her thrombosis manifested with multiple embolic strokes that would not have happened without an ASD with left to right flow.

Pathology

Sein Myint NN, Kunaviktikul W, and **Stark A.** A contemporary understanding of organizational climate in healthcare setting: A concept analysis. *Nurs Forum* 2020; Epub ahead of print. PMID: 33020958. [Full Text](#)

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AIM: The overarching objective of this report is to provide an updated definition of the concept of organizational climate and to strengthen its operational application. **BACKGROUND:** Organizational climate is one of the major contributing factors to the exodus of the nursing workforce from the profession. Extensive research has addressed the impact of "organizational climate" on the nursing workforce; yet variations in the interpretation of the concept calls for an updated definition. **DESIGN:** Walker and Avant's strategy was implemented. **DATA SOURCE:** Data were compiled from Medline and CINAHL, Google search engine, and book chapters. **REVIEW METHOD:** A comprehensive and detailed review of the literature was performed. Nineteen historic publications (1939-2012) and 39 healthcare-related publications (2013-2018) were included in the final review. **RESULTS:** The climate of an organization reflects a set of core values and behaviors that can be used to implement evidence-based leadership and management within the context of the 21st century. We have revised the definition of organizational climate to capture this context. **CONCLUSION:** The perception of a supportive and constructive climate in an organization propels the workforce, independent of ethnic or personal background, to a higher level of productivity and encourages loyalty and workforce stability.

Pathology

Shallal A, Markowitz N, and Tibbetts R. Closing the Brief Case: Cough in an Immunocompromised Patient. *J Clin Microbiol* 2020; 58(11). PMID: 33087543. [Full Text](#)

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Pathology

Shallal A, Markowitz N, and Tibbetts R. The Brief Case: Cough in an Immunocompromised Patient. *J Clin Microbiol* 2020; 58(11). PMID: 33087542. [Full Text](#)

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Pharmacy

Doh J, Hencken L, Mlynarek L, and MacDonald N. Utilization of a Standardized Discharge Checklist to Improve the Transition of Care for Patients Receiving Parenteral Nutrition. *Nutr Clin Pract* 2020; Epub ahead of print. PMID: 33037705. [Full Text](#)

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BACKGROUND: Guidelines recommend using discharge checklists to discharge patients receiving parenteral nutrition (PN). Transition-of-care (TOC) tools have not been extensively studied in the PN population. The purpose of this study is to evaluate the impact of a standardized PN discharge checklist on TOC for PN patients. **METHODS:** This is an Institutional Review Board-approved, retrospective quasi-experimental study of patients discharged receiving PN between January 1, 2014, and May 31, 2018. The primary end point was the completion of a PN discharge bundle (identification of a responsible provider to monitor PN after discharge, meeting daily caloric requirement of 20-35 kcal/kg/d, cycling PN prior to discharge). Secondary end points included documentation of PN discharge checklist components, hospital length of stay, frequency of 30-day hospital encounters, cause of hospital encounters, and time to readmission. **RESULTS:** Fifty encounters were included in the pregroup and postgroup each (n = 100). There was a significant increase in completion of the TOC bundle in the postgroup (54% vs 76%, P = .035), driven by identification of a responsible provider for outpatient PN management (54% vs 82%, P = .005). Other PN discharge checklist components impacted included the following: case manager had the PN prescription for home infusion (50% vs 80%, P = .003), assessment for home glucometer (40% vs 90%, P < .001), and PN plan-of-care note documentation at discharge (18% vs 82%, P < .001). **CONCLUSIONS:** A standardized PN discharge checklist improved completion of discharge bundle.

Pharmacy

Shallal A, Kenney R, and Weinmann A. Missed Vaccine Opportunities to *S. pneumoniae* and Influenza in Patients Admitted During the COVID-19 Pandemic. *Infect Control Hosp Epidemiol* 2020; Epub ahead of print. PMID: 33100230. [Full Text](#)

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Public Health Sciences

Bier A, **Hong X, Cazacu S**, Goldstein H, Rand D, **Xiang C, Jiang W**, Ben-Asher HW, **Attia M**, Brodie A, **She R, Poisson LM**, and Brodie C. miR-504 modulates the stemness and mesenchymal transition of glioma stem cells and their interaction with microglia via delivery by extracellular vesicles. *Cell Death Dis* 2020; 11(10):899. PMID: 33093452. [Full Text](#)

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Glioblastoma (GBM) is a highly aggressive tumor with poor prognosis. A small subpopulation of glioma stem cells (GSCs) has been implicated in radiation resistance and tumor recurrence. In this study we analyzed the expression of miRNAs associated with the functions of GSCs using miRNA microarray analysis of these cells compared with human neural stem cells. These analyses identified gene clusters associated with glioma cell invasiveness, axonal guidance, and TGF- β signaling. miR-504 was significantly downregulated in GSCs compared with NSCs, its expression was lower in GBM compared with normal brain specimens and further decreased in the mesenchymal glioma subtype. Overexpression of miR-504 in GSCs inhibited their self-renewal, migration and the expression of mesenchymal markers. The inhibitory effect of miR-504 was mediated by targeting Grb10 expression which acts as an oncogene in GSCs and GBM. Overexpression of exogenous miR-504 resulted also in its delivery to cocultured microglia by GSC-secreted extracellular vesicles (EVs) and in the abrogation of the GSC-induced polarization of microglia to M2 subtype. Finally, miR-504 overexpression prolonged the survival of mice harboring GSC-derived xenografts and decreased tumor growth. In summary, we identified miRNAs and potential target networks that play a role in the stemness and mesenchymal transition of GSCs and the miR-504/Grb10 pathway as an important regulator of this process. Overexpression of miR-504 exerted antitumor effects in GSCs as well as bystander effects on the polarization of microglia via delivery by EVs.

Public Health Sciences

Bossick AS, Katon JG, Gray KE, Ma EW, and Callegari LS. Concomitant Bilateral Salpingo-Oophorectomy at Hysterectomy: Differences by Race and Menopausal Status in the Veterans Affairs Health Care System, 2007-2014. *J Womens Health (Larchmt)* 2020; Epub ahead of print. PMID: 33095114. [Request Article](#)

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Background: Hysterectomy can be performed with concomitant bilateral salpingo-oophorectomy (BSO) to treat symptomatic pathology of the ovary (e.g., endometriosis) or to prevent ovarian cancer. Our objective was to examine the relationship between race and concomitant BSO by menopausal status in the Veterans Affairs (VA) health care system. **Methods:** This is a longitudinal study utilizing VA administrative data to identify hysterectomies provided or paid for by VA (i.e., source of care) between 2007 and 2014. We defined BSO as removal of both ovaries and fallopian tubes at the time of hysterectomy, identified by International Classification of Diseases-Ninth Revision codes. Covariates included demographic (e.g., ethnicity) and gynecological diagnoses (e.g., endometriosis). We used generalized linear models with a log-link and binomial distribution to estimate associations of race with BSO by menopausal status and source of care. **Results:** We identified 6,785 Veterans with hysterectomies, including 2,320 with concomitant BSO. Overall, Black Veterans were more likely to be single, obese, and undergo abdominal hysterectomy. After adjustment, premenopausal Black Veterans had a 41% lower odds of BSO than their White counterparts (odds ratio [OR]: 0.59, 95% confidence interval [CI]: 0.51-0.68). Stratifying on source of care, these results remained unchanged (provided: OR: 0.61, 95% CI: 0.52-0.72; paid: OR: 0.58, 95% CI: 0.48-0.71). There was insufficient evidence of an association among postmenopausal Veterans. **Conclusions:** Premenopausal Black Veterans are less likely to undergo BSO even after adjustment for salient characteristics. Our findings may have implications for equitable gynecological care for Veterans. Additional research is needed to better understand the role of differential preferences or cancer risk in these racial differences.

Public Health Sciences

Corley DA, Sedki M, Ritzwoller DP, Greenlee RT, **Neslund-Dudas C**, Rendle KA, Honda SA, Schottinger JE, Udaltsova N, Vachani A, Kobrin S, Li CI, and Haas JS. Cancer Screening during COVID-19: A Perspective from NCI's PROSPR consortium. *Gastroenterology* 2020; Epub ahead of print. PMID: 33096099. [Full Text](#)

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Public Health Sciences

Gonzalez H, Imam Z, Wong R, **Li J**, **Lu M**, **Trudeau S**, **Gordon S**, Imam M, and Gish R. Normal alkaline phosphatase levels are dependent on race/ethnicity: National GEP Health and Nutrition Examination Survey data. *BMJ Open Gastroenterol* 2020; 7(1). PMID: 33055108. [Full Text](#)

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OBJECTIVE: The range of normal serum alkaline phosphatase is not well defined. We used data from the National Health and Nutrition Examination Survey from 2009 to 2016 to generate normal ranges for a racially diverse sample of healthy adults. **METHODS:** Respondents 18 years or older were included. Conditions known to elevate alkaline phosphatase were cause for exclusion. Alkaline phosphatase was measured using a colorimetric method based on standardised National Health and Nutrition Examination Survey protocols. Because alkaline phosphatase values were not normally distributed, log transformation was used. We calculated upper limits of normal (97.5 percentile), stratified by sex and race/ethnicity, and 90% CIs for the upper limits of normal. **RESULTS:** 1199 respondents (673 female, 526 male) had body mass index from 18.5 to less than 25. Upper limits of normal were highest among Hispanics (123.2 IU/L (90% CI 110.2 to 136.7) for females; 123.8 IU/L (90% CI 112.0 to 135.1) for males), followed by African Americans (109.9 IU/L (90% CI 97.3 to 122.4) for females; 116.3 IU/L (90% CI 105.0 to 126.1) for males) and whites (97.1 IU/L (90% CI 91.0 to 103.4) for females; 109.6 IU/L (90% CI 102.1 to 116.3) for males). Asian American/Pacific Islander respondents had the lowest results: 93.8 IU/L (90% CI 88.2 to 99.5) for females and 95.3 IU/L (90% CI 88.1 to 102.1) for males. **CONCLUSIONS:** The upper limit of normal alkaline phosphatase varies by race/ethnicity in a large US sample with body mass index of 18.5<25.

Public Health Sciences

Kassem Z, Sitarik A, Levin AM, Lynch SV, Havstad S, Fujimura K, Kozyrskyj A, Ownby DR, Johnson CC, Yong GJM, Wegienka G, and Cassidy-Bushrow AE. Maternal and cord blood vitamin D level and the infant gut microbiota in a birth cohort study. *Matern Health Neonatol Perinatol* 2020; 6:5. PMID: 33101701. [Full Text](#)

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BACKGROUND: Mounting evidence suggests both vitamin D and the early life gut microbiome influence childhood health outcomes. However, little is known about how these two important exposures are related. We aimed to examine associations between plasma 25-hydroxyvitamin D (25[OH]D) levels during pregnancy or at delivery (cord blood) and infant gut microbiota. **METHODS:** Maternal and cord blood 25[OH]D levels were assessed in a sample of pregnant women. Compositional analyses adjusted for race were run on the gut microbiota of their offspring at 1 and 6 months of age. **RESULTS:** Mean prenatal 25(OH)D level was 25.04 ± 11.62 ng/mL and mean cord blood 25(OH)D level was 10.88 ± 6.77 ng/mL. Increasing prenatal 25(OH)D level was significantly associated with decreased richness (p = 0.028) and diversity (p = 0.012) of the gut microbiota at 1 month of age. Both prenatal and cord 25(OH)D were significantly associated with 1 month microbiota composition. A total of 6 operational taxonomic units (OTUs) were significantly associated with prenatal 25(OH)D level (four positively and two negatively) while 11 OTUs were significantly associated with cord 25(OH)D (10 positively and one negatively). Of these, OTU 93 (*Acinetobacter*) and OTU 210 (*Corynebacterium*), were consistently positively associated with maternal and cord 25(OH)D; OTU 64 (*Ruminococcus gnavus*) was positively associated with prenatal 25(OH)D but negatively associated with cord 25(OH)D. **CONCLUSIONS:** Prenatal maternal and cord blood 25(OH)D levels are associated with the early life gut microbiota. Future studies are needed to understand how vitamin D and the microbiome may interact to influence child health.

Public Health Sciences

Lanfear DE, Luzum JA, She R, Gui H, Donahue MP, O'Connor CM, Adams KF, Sanders-van Wijk S, Zeld N, Maeder MT, Sabbah HN, Kraus WE, Brunner-La Rocca HP, Li J, and Williams LK. Polygenic Score for Beta-Blocker Survival Benefit in European Ancestry Patients with Reduced Ejection Fraction Heart Failure. *Circ Heart Fail* 2020; Epub ahead of print. PMID: 33012170. [Full Text](#)

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Background: Beta-blockers (BB) are mainstay therapy for heart failure with reduced ejection fraction (HFrEF). However, individual patient responses to BB vary, which may be partially due to genetic variation. The goal of this study was to derive and validate the first polygenic response predictor (PRP) for BB survival benefit in HFrEF patients. Methods: Derivation and validation analyses were performed in n=1,436 total HF patients of European descent and with EF <50%. The PRP was derived in a random subset of the Henry Ford Pharmacogenomic Registry (HFPGR; n=248), and then validated in a meta-analysis of the remaining patients from HFPGR (n=247), the TIME-CHF (n=431), and HF-ACTION trial (n=510). The PRP was constructed from a genome-wide analysis of BB*genotype interaction predicting time to all-cause mortality, adjusted for MAGGIC score, genotype, level of BB exposure, and BB propensity score. Results: Five-fold cross-validation summaries out to 1000 SNPs identified optimal prediction with a 44 SNP score and cutoff at the 30th percentile. In validation testing (n=1188) greater BB exposure was associated with reduced all-cause mortality in patients with low-PRP score (n=251; HR=0.19 [95% CI=0.04-0.51], p=0.0075), but not high-PRP score (n=937; HR=0.84 [95% CI=0.53-1.3], p=0.448), a difference that was statistically significant (p interaction =0.0235). Results were consistent regardless of atrial fibrillation, EF ($\leq 40\%$ vs. 41-50%), or when examining cardiovascular death. Conclusions: Among patients of European ancestry with HFrEF, a PRP distinguished patients who derived substantial survival benefit from BB exposure from a larger group that did not. Additional work is needed prospectively test clinical utility and to develop PRPs for other population groups and other medications.

Public Health Sciences

Zhu S, Khalil R, Altairy O, Burmeister C, Dimitrova I, and Elshaikh M. Increased risk of recurrence in early-stage endometrial carcinoma after delays in adjuvant radiation treatment. *Int J Gynecol Cancer* 2020; Epub ahead of print. PMID: 33087415. [Full Text](#)

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OBJECTIVE: The benefits of adjuvant radiation treatment after hysterectomy have been confirmed in select patients with early-stage endometrial carcinoma. The goal of this study was to evaluate the

prognostic impact of the time interval between hysterectomy and starting adjuvant radiation treatment in patients with early-stage endometrial carcinoma. **METHODS:** Our database was searched for women with early-stage endometrioid endometrial cancer who received adjuvant radiation therapy after hysterectomy. The patients were classified into two groups based on the time interval to adjuvant radiation therapy (≤ 8 weeks or >8 weeks) after hysterectomy. Recurrence-free survival, disease-specific survival, and overall survival were compared between the two groups. **RESULTS:** Four hundred and sixty patients were identified. Median follow-up was 70.5 months (range 1-360). One hundred and seventy-six patients (38%) were 2009 International Federation of Gynecology and Obstetrics stage IA, 207 (45%) stage IB, and 77 (17%) stage II. Three hundred and fifty-four women (77%) received adjuvant radiation therapy within 8 weeks after hysterectomy. There was no statistically significant difference between the two groups in baseline demographics, disease and treatment characteristics, except for the modality of adjuvant radiation therapy. Patients who received adjuvant radiation therapy within 8 weeks experienced significantly less disease recurrence (9% vs 18%; $p=0.01$) and particularly less isolated vaginal recurrence (0% vs 6%, $p=0.04$). Five-year recurrence-free survival was 89% versus 80% ($p=0.04$), 5-year disease-specific survival was 93% for both groups, and 5-year overall survival was 86% versus 85% for patients who received adjuvant radiation therapy ≤ 8 and >8 weeks, respectively ($p=0.88$). **CONCLUSION:** Our study suggests that delaying adjuvant radiation therapy beyond 8 weeks after hysterectomy is associated with significantly more cancer recurrences for women with early-stage endometrial carcinoma.

Pulmonary and Critical Care Medicine

Berry LL, and **Adawi Awdish RL**. Health Care Organizations Should Be as Generous as Their Workers. *Ann Intern Med* 2020; Epub ahead of print. PMID: 33076692. [Full Text](#)

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Providing excellent medical care, especially during the current pandemic, demands the generosity of health care workers—requiring them to make sacrifices while exhibiting emotional strength, resilience, and compassion. This article describes how institutional generosity is critical in supporting health care workers and in enabling health care organizations to succeed and thrive.

Pulmonary and Critical Care Medicine

Nemeh H, Coba V, Chulkov M, Gupta A, Yeldo N, Chamogeorgakis T, Tanaka D, Allenspach L, Simanovski J, and Shanti C. Lung Transplantation for the Treatment of Vaping Induced, Irreversible, End Stage Lung Injury. *Ann Thorac Surg* 2020; Epub ahead of print. PMID: 33130115. [Full Text](#)

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Recently, there has been a rise in the incidence of E-cigarettes/Vaping Associated Lung Injury (EVALI) in the United States mostly involving Tetrahydrocannabinol (THC)(1). Present treatment strategies for EVALI are aimed at controlling the inflammatory and infectious etiologies in addition to supportive care(2). While most patients improve with supportive measures(3,4) the long-term pulmonary effects of this illness are still not well defined. In this report, we describe a case of EVALI resulting in progressive, irreversible destruction of the lung parenchyma that was treated with double lung transplantation.

Radiation Oncology

Dumas M, Laugeman E, Sevak P, Snyder KC, Mao W, Chetty IJ, Ajlouni M, and Wen N. Technical Note: Comparison of the internal target volume (ITV) contours and dose calculations on 4DCT, average CBCT, and 4DCBCT imaging for lung stereotactic body radiation therapy (SBRT). *J Appl Clin Med Phys* 2020; Epub ahead of print. PMID: 33044040. [Full Text](#)

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PURPOSE: To investigate the differences between internal target volumes (ITVs) contoured on the simulation 4DCT and daily 4DCBCT images for lung cancer patients treated with stereotactic body radiotherapy (SBRT) and determine the dose delivered on 4D planning technique. **METHODS:** For nine patients, 4DCBCTs were acquired before each fraction to assess tumor motion. An ITV was contoured on each phase of the 4DCBCT and a union of the 10 ITVs was used to create a composite ITV. Another ITV was drawn on the average 3DCBCT (avgCBCT) to compare with current clinical practice. The Dice coefficient, Hausdorff distance, and center of mass (COM) were averaged over four fractions to compare the ITVs contoured on the 4DCT, avgCBCT, and 4DCBCT for each patient. Planning was done on the average CT, and using the online registration, plans were calculated on each phase of the 4DCBCT and on the avgCBCT. Plan dose calculations were tested by measuring ion chamber dose in the CIRS lung phantom. **RESULTS:** The Dice coefficients were similar for all three comparisons: avgCBCT-to-4DCBCT (0.7 ± 0.1), 4DCT-to-avgCBCT (0.7 ± 0.1), and 4DCT-to-4DCBCT (0.7 ± 0.1); while the mean COM differences were also comparable (2.6 ± 2.2 mm, 2.3 ± 1.4 mm, and 3.1 ± 1.1 mm, respectively). The Hausdorff distances for the comparisons with 4DCBCT (8.2 ± 2.9 mm and 8.1 ± 3.2 mm) were larger than the comparison without (6.5 ± 2.5 mm). The differences in ITV D95% between the treatment plan and avgCBCT calculations were $4.3 \pm 3.0\%$ and $-0.5 \pm 4.6\%$, between treatment plan and 4DCBCT plans, respectively, while the ITV V100% coverages were $99.0 \pm 1.9\%$ and $93.1 \pm 8.0\%$ for avgCBCT and 4DCBCT, respectively. **CONCLUSION:** There is great potential for 4DCBCT to evaluate the extent of tumor motion before treatment, but image quality challenges the clinician to consistently delineate lung target volumes.

Radiation Oncology

Higgins KA, Simone CB, 2nd, Amini A, **Chetty IJ**, Donington J, Edelman MJ, Chun SG, Kestin LL, **Movsas B**, Rodrigues GB, Rosenzweig KE, Slotman BJ, **Rybkin, II**, Wolf A, and Chang JY. American Radium Society™, Appropriate Use Criteria on Radiation Therapy for Extensive-stage Small Cell Lung Cancer. *J Thorac Oncol* 2020; Epub ahead of print. PMID: 33011389. [Request Article](#)

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BACKGROUND: Standard of care therapy for extensive-stage small cell lung cancer (ES-SCLC) has recently changed with the results of two large, randomized trials demonstrating improved survival with the addition of immunotherapy to first-line platinum/etoposide chemotherapy. This has led to lack of clarity around the role of consolidative thoracic radiation and prophylactic (PCI) in the setting of chemo-immunotherapy. **METHODS:** The American Radium Society (ARS) Appropriate Use Criteria are evidence-based guidelines for specific clinical conditions that are reviewed by a multidisciplinary expert panel. The guidelines include a review and analysis of current evidence with application of consensus methodology (modified Delphi) to rate the appropriateness of treatments recommended by the panel for ES-SCLC. **CONCLUSIONS:** Current evidence supports either PCI or surveillance with magnetic resonance imaging (MRI) every 3 months for optimal management of the brain. Patients with brain metastases should receive whole brain radiation, 30 Gy in 10 fractions. Consolidative thoracic radiation

can be considered in select cases with the recommended dose ranging from 30-54 Gy, with this recommendation driven by expert opinion due to the limited strength of evidence as clinical trials addressing this question remain ongoing.

Radiation Oncology

Margalit DN, Sacco AG, Cooper JS, Ridge JA, Bakst RL, Beadle BM, Beitler JJ, **Chang SS**, Chen AM, Galloway TJ, Koyfman SA, Mita C, Robbins JR, Tsai CJ, Truong MT, Yom SS, and **Siddiqui F**. Systematic review of postoperative therapy for resected squamous cell carcinoma of the head and neck: Executive summary of the American Radium Society appropriate use criteria. *Head Neck* 2020; Epub ahead of print. PMID: 33098180. [Full Text](#)

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Countway Library, Harvard Medical School, Boston, Massachusetts, USA.
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BACKGROUND: The aims of this systematic review are to (a) evaluate the current literature on the impact of postoperative therapy for resected squamous cell carcinoma of the head and neck (SCCHN) on oncologic and non-oncologic outcomes and (b) identify the optimal evidence-based postoperative therapy recommendations for commonly encountered clinical scenarios. **METHODS:** An analysis of the medical literature from peer-reviewed journals was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline. Prospective studies and methodology-based systematic reviews and meta-analyses of postoperative therapy for SCCHN were identified by searching Medline (OVID) and EMBASE (Elsevier) using controlled vocabulary terms (ie, National Library of Medicine Medical Subject Headings [MeSH], Emtree). Study screening and selection was performed with Covidence software and full-text review. The RAND/UCLA appropriateness method was used by the expert panel to rate the appropriate use of postoperative therapy, and the modified Delphi method was used to come to consensus. **RESULTS:** A total of 5660 studies were identified and screened using the title and abstract, leading to 201 studies assessed for relevance using full-text review. After limitation to the eligibility criteria, 101 studies from 1977 to 2020 were identified, including 77 with oncologic endpoints and 24 with function and quality of life endpoints. All studies reported staging prior to the implementation of American Joint Committee on Cancer (AJCC-8). **CONCLUSIONS:** Prospective clinical studies and systematic reviews identified through the PRISMA systematic review provided good evidence for consensus statements regarding the appropriate use of postoperative therapy for resected SCCHN. Further research is needed in domains where consensus by the expert panel could not be achieved for the appropriateness of specific postoperative therapeutic interventions.

Radiation Oncology

Morris ED, **Aldridge K**, **Ghanem AI**, **Zhu S**, and Glide-Hurst CK. Incorporating sensitive cardiac substructure sparing into radiation therapy planning. *J Appl Clin Med Phys* 2020; Epub ahead of print. PMID: 33073454. [Full Text](#)

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PURPOSE: Rising evidence suggests that cardiac substructures are highly radiosensitive. However, they are not routinely considered in treatment planning as they are not readily visualized on treatment planning CTs (TPCTs). This work integrated the soft tissue contrast provided by low-field MRIs acquired on an MR-linac via image registration to further enable cardiac substructure sparing on TPCTs. **METHODS:** Sixteen upper thoracic patients treated at various breathing states (7 end-exhalation, 7 end-inhalation, 2 free-breathing) on a 0.35T MR-linac were retrospectively evaluated. A hybrid MR/CT atlas and a deep learning three-dimensional (3D) U-Net propagated 13 substructures to TPCTs. Radiation oncologists revised contours using registered MRIs. Clinical treatment plans were re-optimized and evaluated for beam arrangement modifications to reduce substructure doses. Dosimetric assessment included mean and maximum (0.03cc) dose, left ventricular volume receiving 5Gy (LV-V5), and other clinical endpoints. As metrics of plan complexity, total MU and treatment time were evaluated between approaches. **RESULTS:** Cardiac sparing plans reduced the mean heart dose (mean reduction 0.7 ± 0.6 , range 0.1 to 2.5 Gy). Re-optimized plans reduced left anterior descending artery (LADA) mean and LADA(0.03cc) (0.0-63.9% and 0.0 to 17.3 Gy, respectively). LV(0.03cc) was reduced by >1.5 Gy for 10 patients while 6 cases had large reductions ($>7\%$) in LV-V5. Left atrial mean dose was equivalent/reduced in all sparing plans (mean reduction 0.9 ± 1.2 Gy). The left main coronary artery was better spared in all cases for mean dose and D(0.03cc). One patient exhibited >10 Gy reduction in D(0.03cc) to four substructures. There was no statistical difference in treatment time and MU, or clinical endpoints to the planning target volume, lung, esophagus, or spinal cord after re-optimization. Four patients benefited from new beam arrangements, leading to further dose reductions. **CONCLUSIONS:** By introducing 0.35T MRIs acquired on an MR-linac to verify cardiac substructure segmentations for CT-based treatment planning, an opportunity was presented for more effective sparing with limited increase in plan complexity. Validation in a larger cohort with appropriate margins offers potential to reduce radiation-related cardiotoxicities.

Radiation Oncology

Tsai CJ, Galloway TJ, Margalit DN, Bakst RL, Beadle BM, Beitler JJ, **Chang S**, Chen A, Cooper J, Koyfman SA, Ridge JA, Robbins J, Truong MT, Yom SS, and **Siddiqui F**. Ipsilateral radiation for squamous cell carcinoma of the tonsil: American Radium Society appropriate use criteria executive summary. *Head Neck* 2020; Epub ahead of print. PMID: 33068064. [Full Text](#)

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BACKGROUND: We conducted the current systemic review to provide up-to-date literature summary and optimal evidence-based recommendations for ipsilateral radiation for squamous cell carcinoma of the tonsil. **METHODS:** We performed literature search of peer-reviewed journals through PubMed. The search strategy and subject-specific keywords were developed based on the expert panel's consensus. Articles published from January 2000 to May 2020 with full text available on PubMed and restricted to the English language and human subjects were included. Several prespecified search terms were used to identify relevant publications and additional evidence published since the initial American College of Radiology Appropriateness Criteria Ipsilateral Tonsil Radiation recommendation was finalized in 2012. The full bibliographies of identified articles were reviewed and irrelevant studies were removed.

RESULTS: The initial search and review returned 46 citations. The authors added three citations from bibliographies, websites, or books not found in the literature search. Of the 49 citations, 30 citations were retained for further detailed review, and 14 of them were added to the evidence table. Articles were removed from the bibliography if they were not relevant or generalizable to the topic, or focused on unknown primary disease. Several commonly encountered clinical case variants were created and panelists anonymously rated each treatment recommendation. The results were reviewed and disagreements discussed. **CONCLUSIONS:** The panel provided updated evidence and recommendations for ipsilateral radiation for squamous cell carcinoma of the tonsil in the setting of primary radiation-based therapy and postoperative adjuvant radiotherapy. This committee did not reach agreements for some case variants due to a lack of strong evidence supporting specific treatment decisions, indicating a further need for research in these topics.

Radiation Oncology

Vscariello I, Evans S, Parker S, Schofield D, **Miller B**, Gardner S, Fong de Los Santos L, Hallemeier C, Jordan L, Kim E, and Ford E. A multi-institutional assessment of COVID-19-related risk in radiation oncology. *Radiother Oncol* 2020; Epub ahead of print. PMID: 33096163. [Full Text](#)

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PURPOSE: The COVID-19 pandemic has presented challenges to delivering safe and timely care for cancer patients. The oncology community has undertaken substantial workflow adaptations to reduce transmission risk for patients and providers. While various control measures have been proposed and implemented, little is known about their impact on safety of the radiation oncology workflow and potential for transmission. The objective of this study was to assess potential safety impacts of control measures employed during the COVID-19 pandemic. **METHODS:** A multi-institutional study was undertaken to assess the risks of pandemic-associated workflow adaptations using failure mode and effects analysis (FMEA). Failure modes were identified and scored using FMEA formalism. FMEA scores were used to identify highest-risk aspects of the radiation therapy process. The impact of control measures on overall risk was quantified. Agreement among institutions was evaluated. **RESULTS:** 33 failure modes and 22 control measures were identified. Control measures resulted in risk score reductions for 22 of the failure modes, with the largest reductions from screening of patients and staff, requiring use of masks, and regular cleaning of patient areas. The median risk score for all failure modes was reduced from 280 to 168. There was high institutional agreement for 90.3% of failure modes but only 47% of control measures. **CONCLUSIONS:** COVID-related risks are similar across oncology practices in this study. While control measures can reduce risk, their use varied. The effectiveness of control measures on risk may guide selection of the highest-impact workflow adaptations to ensure safe care in oncology.

Radiation Oncology

Zhu S, Khalil R, Altairy O, Burmeister C, Dimitrova I, and Elshaikh M. Increased risk of recurrence in early-stage endometrial carcinoma after delays in adjuvant radiation treatment. *Int J Gynecol Cancer* 2020; Epub ahead of print. PMID: 33087415. [Full Text](#)

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OBJECTIVE: The benefits of adjuvant radiation treatment after hysterectomy have been confirmed in select patients with early-stage endometrial carcinoma. The goal of this study was to evaluate the prognostic impact of the time interval between hysterectomy and starting adjuvant radiation treatment in

patients with early-stage endometrial carcinoma. **METHODS:** Our database was searched for women with early-stage endometrioid endometrial cancer who received adjuvant radiation therapy after hysterectomy. The patients were classified into two groups based on the time interval to adjuvant radiation therapy (≤ 8 weeks or >8 weeks) after hysterectomy. Recurrence-free survival, disease-specific survival, and overall survival were compared between the two groups. **RESULTS:** Four hundred and sixty patients were identified. Median follow-up was 70.5 months (range 1-360). One hundred and seventy-six patients (38%) were 2009 International Federation of Gynecology and Obstetrics stage IA, 207 (45%) stage IB, and 77 (17%) stage II. Three hundred and fifty-four women (77%) received adjuvant radiation therapy within 8 weeks after hysterectomy. There was no statistically significant difference between the two groups in baseline demographics, disease and treatment characteristics, except for the modality of adjuvant radiation therapy. Patients who received adjuvant radiation therapy within 8 weeks experienced significantly less disease recurrence (9% vs 18%; $p=0.01$) and particularly less isolated vaginal recurrence (0% vs 6%, $p=0.04$). Five-year recurrence-free survival was 89% versus 80% ($p=0.04$), 5-year disease-specific survival was 93% for both groups, and 5-year overall survival was 86% versus 85% for patients who received adjuvant radiation therapy ≤ 8 and >8 weeks, respectively ($p=0.88$). **CONCLUSION:** Our study suggests that delaying adjuvant radiation therapy beyond 8 weeks after hysterectomy is associated with significantly more cancer recurrences for women with early-stage endometrial carcinoma.

Rheumatology

Coit P, Ortiz-Fernandez L, Lewis EE, McCune WJ, **Maksimowicz-McKinnon K**, and Sawalha AH. A longitudinal and transancestral analysis of DNA methylation patterns and disease activity in lupus patients. *JCI Insight* 2020; Epub ahead of print. PMID: 33108347. [Full Text](#)

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Epigenetic dysregulation is implicated in the pathogenesis of lupus. We performed a longitudinal analysis to assess changes in DNA methylation in lupus neutrophils over 4 years of follow up and across disease activity levels using 229 patient samples. We demonstrate that DNA methylation profiles in lupus are partly determined by ancestry-associated genetic variations and are highly stable over time. DNA methylation levels in two CpG sites correlated significantly with changes in lupus disease activity. Progressive demethylation in SNX18 was observed with increasing disease activity in African-American patients. Importantly, demethylation of a CpG site located within GALNT18 was associated with the development of active lupus nephritis. Differentially methylated genes between African-American and European-American lupus patients include type I interferon-response genes such as IRF7 and IFI44, and genes related to the NF κ B pathway. TREML4, which plays a vital role in toll-like receptor signaling, was hypomethylated in African-American patients and demonstrated a strong cis-meQTL effect among 8855 cis-meQTL associations identified in our study.

Rheumatology

Liaqat H, Shirvanian N, Ammad Ud Din M, and **Amin A**. Cocaine-related vasculitis. *Clinical Case Reports* 2020; Epub ahead of print. PMID: Not assigned. [Full Text](#)

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Patients presenting with pancytopenia and a painful purpuric rash should be evaluated for levamisole-induced vasculitis and counseled about cocaine cessation as continued exposure can lead to permanent deformity of the involved areas.

Sleep Medicine

Marques DR, Gomes AA, Clemente V, **Drake CL, Roth T**, Morin CM, and de Azevedo MHP. Typologies of individuals vulnerable to insomnia: a two-step cluster analysis. *Sleep and Biological Rhythms* Epub ahead of print. PMID: Not assigned. [Request Article](#)

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Research and clinical practice have demonstrated that patients with insomnia are a heterogeneous population. As such, it is important to understand and differentiate the potential sub-groups among insomnia patients as well as individuals at risk for insomnia. Questionnaires completed by 291 students of both sexes and at risk for insomnia (FIRST scale score ≥ 22) were analyzed (age range 17-24 years). Two-step cluster analyses comprising all the valid cases (N = 291) were performed to analyze the phenotypes of individuals vulnerable to insomnia separately for men and women. The results showed that men and women present different psychological profiles. Among men, it was possible to distinguish two clusters: one with relatively low scores in negative psychological variables and high positive affect and another with high scores in negative psychological variables and low scores in positive affect. Among women, three clusters were observed: two resembling the ones found for the male sample and one additional cluster encompassing individuals with moderate scores on all of the measures. However, it is possible that this additional group in women may be due to the larger sample size. The current study supports the idea that among individuals at risk for insomnia, one can discriminate different profiles. Sex-related differences should be further investigated in the future.

Sleep Medicine

Mohindra M, Bird S, Charest J, Huyghe T, and Calleja-Gonzalez J. Urgent wake up call for the NBA. *J Clin Sleep Med* 2020; Epub ahead of print. PMID: 33112229. [Full Text](#)

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Frequent air travel and the condensed game schedule typical of a National Basketball Association (NBA) teams during the season, often results in accompanying sleep disturbances related to sleep length, sleep quality and sleep timing (with highly harmful impacts on health, both physical and mental). These issues are not only problematic for NBA players, but also the coaches, training staff and management support. In this narrative review, we summarize the detrimental effects that this travel and game schedule could have on NBA team member's sleep, as well as their physical and mental health. Multiple peer-reviewed articles address the role of sleep in athletic performance and health, however, to date, the literature focused on sleep-related issues that are unique to the NBA schedule is scarce. Firstly, this review addresses the impact of the NBA schedule, outlining the number of games, and the travel involved (number of flights, the timing of flights, timings of arrival at destination and hotel), we also outline a typical daily NBA travel schedule, providing the reader a glimpse of what this encompasses. Secondly, we provide a brief overview of sleep science and discuss specific applications related to the NBA. Finally, we provide comment on the unique current situation of the NBA "bubble". Based on this review, there appears to be considerable scope for further investigation of the acute and chronic effects of sleep disturbances concerning the NBA travel and game schedule. Sleep science recommendations need to inform practice,

target sleep interventions and personalized protocols designed to enhance sleep health that can be incorporated at the organizational level.

Sleep Medicine

Swanson LM, **Kalmbach DA**, Raglan GB, and O'Brien LM. Perinatal Insomnia and Mental Health: a Review of Recent Literature. *Curr Psychiatry Rep* 2020; 22(12):73. PMID: 33104878. [Full Text](#)

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PURPOSE OF REVIEW: The perinatal period is a time of high risk for insomnia and mental health conditions. The purpose of this review is to critically examine the most recent literature on perinatal insomnia, focusing on unique features of this period which may confer specific risk, associations with depression and anxiety, and emerging work on perinatal insomnia treatment. **RECENT FINDINGS:** A majority of perinatal women experience insomnia, which may persist for years, and is associated with depression and anxiety. Novel risk factors include personality characteristics, nocturnal perinatal-focused rumination, and obesity. Mindfulness and physical activity may be protective. Cognitive-behavioral therapy for insomnia is an effective treatment. Perinatal insomnia is exceedingly common, perhaps due to factors unique to this period. Although closely linked to perinatal mental health, more work is needed to establish causality. Future work is also needed to establish the role of racial disparities, tailor treatments, and determine whether insomnia treatment improves perinatal mental health.

Sleep Medicine

Weaver TE, Mathias SD, Crosby RD, Bron M, Bujanover S, Menno D, Villa KF, and **Drake C**.

Relationship between sleep efficacy endpoints and measures of functional status and health-related quality of life in participants with narcolepsy or obstructive sleep apnea treated for excessive daytime sleepiness. *J Sleep Res* 2020; Epub ahead of print. PMID: 33051943. [Full Text](#)

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This study examined the correlation between improvements in excessive daytime sleepiness in participants with obstructive sleep apnea or narcolepsy and changes in functional status, work productivity and health-related quality of life. Data from two 12-week randomized controlled trials of solriamfetol were analyzed. Participants completed the Epworth Sleepiness Scale, 10-item Functional Outcomes of Sleep Questionnaire, Work Productivity and Activity Impairment questionnaire and 36-Item Short Form Health Survey and performed the Maintenance of Wakefulness Test at baseline and weeks 4, 8 and 12. Patient Global Impression of Change was assessed at weeks 4, 8 and 12. Pearson correlations were calculated for change in scores from baseline to week 12. For both studies, changes in the 10-item Functional Outcomes of Sleep Questionnaire were highly correlated (absolute value >0.5) with changes in Epworth Sleepiness Scale scores; changes in multiple domain scores of the 36-Item Short Form Health Survey and Work Productivity and Activity Impairment questionnaire were moderately correlated (0.3-0.5) with changes in Epworth Sleepiness Scale scores in both studies and highly correlated for participants with narcolepsy. Changes in Maintenance of Wakefulness Test scores correlated moderately with changes in Epworth Sleepiness Scale scores in both studies. At week 12, Patient Global Impression of

Change ratings correlated highly with Epworth Sleepiness Scale and 10-item Functional Outcomes of Sleep Questionnaire scores for both disorders. Other correlations were low. Self-reported assessments of sleepiness and global improvement appear to be more strongly correlated with measures of functioning and health-related quality of life than objectively assessed sleepiness.

Surgery

D'John M, and **Jabbar F**. Primary gallbladder paraganglioma: A case report and review of literature. *Int J Surg Case Rep* 2020; 75:451-453. PMID: 33076192. [Full Text](#)

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INTRODUCTION: Paragangliomas are tumors arising from paraganglia of the autonomic nervous system. They are rare tumors and occurrence inside the gallbladder is exceptionally rare. Biliary paragangliomas are thought to be associated with the parasympathetic fibers and are therefore non-functioning and benign. There are less than 10 cases reported in literature and majority are found incidentally upon cholecystectomy. There is no specific treatment for these tumors and resection is considered sufficient. **CASE PRESENTATION:** 63 year old female presented with recurrent biliary colic exacerbated by fatty food. She underwent imaging work up that was consistent with biliary dyskinesia. She underwent uneventful elective laparoscopic cholecystectomy and was doing well post-operatively. Pathology report was significant for chronic cholecystitis, no calculi, and a small focus of paraganglioma. **DISCUSSION:** Little is known about primary gallbladder paragangliomas. Due to the non-functioning nature of these tumors there are felt to be benign. We know the paraganglia of the gallbladder consists of both parasympathetic and sympathetic fibers. The sympathetic paragangliomas tend to act similar to pheochromocytomas and thus have malignant potential. **CONCLUSION:** We presented a case in which a primary gallbladder paraganglioma was identified incidentally in a patient who presented with symptomatic biliary dyskinesia. Due to the rarity of primary gallbladder paraganglioma and limited reported cases, optimal follow up remains unknown.

Surgery

Decker JT, **Kandagatla P**, Wan L, Bernstein R, Ma JA, Shea LD, and Jeruss JS. Cyclin E overexpression confers resistance to trastuzumab through noncanonical phosphorylation of SMAD3 in HER2+ breast cancer. *Cancer Biol Ther* 2020; Epub ahead of print. PMID: 33054513. [Request Article](#)

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The efficacy of trastuzumab, a treatment for HER2+ breast cancer, can be limited by the development of resistance. Cyclin E (CCNE) overexpression has been implicated in trastuzumab resistance. We sought to uncover a potential mechanism for this trastuzumab resistance and focused on a model of CCNE overexpressing HER2+ breast cancer and noncanonical phosphorylation of the TGF- β signaling protein, SMAD3. Network analysis of transcriptional activity in a HER2+, CCNE overexpressing, trastuzumab-resistant cell line (BT474R2) identified decreased SMAD3 activity was associated with treatment resistance. Immunoblotting showed SMAD3 expression was significantly downregulated in BT474R2 cells ($p < .01$), and noncanonical phosphorylation of SMAD3 was increased in these CCNE-overexpressing cells. Also, in response to CDK2 inhibition, expression patterns linked to restored canonical SMAD3 signaling, including decreased cMyc and increased cyclin-dependent inhibitor, p15, were identified. The BT474R2 cell line was modified through overexpression of SMAD3 (BT474R2-SMAD3), a mutant construct resistant to CCNE-mediated noncanonical phosphorylation of SMAD3 (BT474R2-5M), and a control (BT474R2-Blank). In vitro studies examining the response to trastuzumab showed increased sensitivity to treatment for BT474R2-5M cells. These findings were then validated in NSG mice inoculated with BT474R2-5M cells or BT474R2 control cells. After treatment with trastuzumab, the NSG mice inoculated with BT474R2-5M cells developed significantly lower tumor volumes ($p < .001$), when

compared to mice inoculated with BT474R2 cells. Taken together, these results indicate that for patients with HER2+ breast cancer, a mechanism of CCNE-mediated trastuzumab resistance, regulated through noncanonical SMAD3 phosphorylation, could be treated with CDK2 inhibition to help enhance the efficacy of trastuzumab therapy.

Surgery

Flum DR, Davidson GH, Monsell SE, Shapiro NI, Odom SR, Sanchez SE, Drake FT, Fischkoff K, **Johnson J, Patton JH**, Evans H, Cuschieri J, Sabbatini AK, Faine BA, Skeete DA, Liang MK, Sohn V, McGrane K, Kutcher ME, Chung B, Carter DW, Ayoung-Chee P, Chiang W, Rushing A, Steinberg S, Foster CS, Schaezel SM, Price TP, Mandell KA, Ferrigno L, Salzberg M, DeUgarte DA, Kaji AH, Moran GJ, Saltzman D, Alam HB, Park PK, Kao LS, Thompson CM, Self WH, Yu JT, Wiebusch A, Winchell RJ, Clark S, Krishnadasan A, Fannon E, Lavalley DC, Comstock BA, Bizzell B, Heagerty PJ, Kessler LG, and Talan DA. A Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis. *N Engl J Med* 2020; Epub ahead of print. PMID: 33017106. [Full Text](#)

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BACKGROUND: Antibiotic therapy has been proposed as an alternative to surgery for the treatment of appendicitis. **METHODS:** We conducted a pragmatic, nonblinded, noninferiority, randomized trial comparing antibiotic therapy (10-day course) with appendectomy in patients with appendicitis at 25 U.S. centers. The primary outcome was 30-day health status, as assessed with the European Quality of Life-5 Dimensions (EQ-5D) questionnaire (scores range from 0 to 1, with higher scores indicating better health status; noninferiority margin, 0.05 points). Secondary outcomes included appendectomy in the antibiotics group and complications through 90 days; analyses were prespecified in subgroups defined according to the presence or absence of an appendicolith. **RESULTS:** In total, 1552 adults (414 with an appendicolith) underwent randomization; 776 were assigned to receive antibiotics (47% of whom were not hospitalized for the index treatment) and 776 to undergo appendectomy (96% of whom underwent a laparoscopic procedure). Antibiotics were noninferior to appendectomy on the basis of 30-day EQ-5D scores (mean difference, 0.01 points; 95% confidence interval [CI], -0.001 to 0.03). In the antibiotics group, 29% had undergone appendectomy by 90 days, including 41% of those with an appendicolith and 25% of those without an appendicolith. Complications were more common in the antibiotics group than in the appendectomy group (8.1 vs. 3.5 per 100 participants; rate ratio, 2.28; 95% CI, 1.30 to 3.98); the higher rate in the antibiotics group could be attributed to those with an appendicolith (20.2 vs. 3.6 per 100 participants; rate ratio, 5.69; 95% CI, 2.11 to 15.38) and not to those without an appendicolith (3.7 vs. 3.5 per 100 participants; rate ratio, 1.05; 95% CI, 0.45 to 2.43). The rate of serious adverse events was 4.0 per 100 participants in the antibiotics group and 3.0 per 100 participants in the appendectomy group (rate ratio, 1.29; 95% CI, 0.67 to 2.50). **CONCLUSIONS:** For the treatment of appendicitis, antibiotics were noninferior to appendectomy on the basis of results of a standard health-status measure. In the antibiotics group, nearly 3 in 10 participants had undergone appendectomy by 90 days. Participants with an appendicolith were at a higher risk for appendectomy and for complications than those without an

appendicolith. (Funded by the Patient-Centered Outcomes Research Institute; CODA ClinicalTrials.gov number, NCT02800785.).

Surgery

Kitajima T, Shamaa T, Hibi T, Moonka D, Sapisochin G, Abouljoud MS, and Nagai S. Response to: "Surgical Volume Alone Does Not Determine Outcome Following Liver Transplant for Perihilar Cholangiocarcinoma". *Ann Surg Oncol* 2020; Epub ahead of print. PMID: 33063257. [Full Text](#)

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Surgery

Nemeh H, Coba V, Chulkov M, Gupta A, Yeldo N, Chamogeorgakis T, Tanaka D, Allenspach L, Simanovski J, and Shanti C. Lung Transplantation for the Treatment of Vaping Induced, Irreversible, End Stage Lung Injury. *Ann Thorac Surg* 2020; Epub ahead of print. PMID: 33130115. [Full Text](#)

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Recently, there has been a rise in the incidence of E-cigarettes/Vaping Associated Lung Injury (EVALI) in the United States mostly involving Tetrahydrocannabinol (THC)(1). Present treatment strategies for EVALI are aimed at controlling the inflammatory and infectious etiologies in addition to supportive care(2). While most patients improve with supportive measures(3,4) the long-term pulmonary effects of this illness are still not well defined. In this report, we describe a case of EVALI resulting in progressive, irreversible destruction of the lung parenchyma that was treated with double lung transplantation.

Surgery

Rodgers SA, Suneja A, Yoshida A, Abouljoud MS, and Otrrock ZK. Paradoxical embolic strokes in a liver transplant recipient with atrial septal defect undergoing therapeutic plasma exchange. *J Clin Apher* 2020; Epub ahead of print. PMID: 33058311. [Full Text](#)

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Therapeutic plasma exchange (TPE) is a technique used to separate blood components into layers based on their density difference, thus removing plasma and exchanging it with replacement fluids. A variety of adverse reactions has been described during TPE. Thrombotic events, especially strokes, are extremely rare complications of TPE. Our patient was a 55-year-old female with history of decompensated nonalcoholic steatohepatitis (NASH) liver cirrhosis. She underwent an orthotopic liver transplant (OLT) that was complicated with asystole during reperfusion. Cardiac workup revealed a new atrial septal defect (ASD) with left to right flow. Within the first 5 days after surgery, she developed refractory and persistent hyperbilirubinemia, with total bilirubin levels as high as 42 mg/dL. Our plasmapheresis service was consulted to initiate TPE. Towards the end of the first and only session of TPE, the patient developed hypoxia and left-sided hemiplegia. Stroke response was initiated, and the patient was intubated. MRI done 24 hours after the incident showed multiple acute small embolic infarcts scattered within the bilateral

cerebral and cerebellar hemispheres. Bilateral lower and upper extremities venous duplex studies were positive for acute left internal jugular (IJ) vein thrombosis. Patient was treated with anticoagulation and the IJ catheter was removed. Patient also had closure of her ASD. On last follow up, she was doing well with complete reversal of neurologic deficits and stable liver function. Our patient had an uncommon complication of TPE. Her thrombosis manifested with multiple embolic strokes that would not have happened without an ASD with left to right flow.

Surgery

Shrivastava P, Prashar R, Khoury N, Patel A, Yedula S, Kitajima T, Nagai S, and Samaniego M. Acute Kidney Injury in a Predominantly African American Cohort of Kidney Transplant Recipients With COVID-19 Infection. *Transplantation* 2020; Epub ahead of print. PMID: 33093403. [Full Text](#)

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Renal involvement in severe or critical acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is frequent. Acute kidney injury (AKI) in African American (AA) kidney transplant recipients (KTRs) with COVID-19 is not well described. We report our experience with a predominantly AA cohort (79%) of KTRs with COVID-19 infections in the Detroit Metropolitan area. METHODS: In this retrospective, single-center study, we identified 39 KTRs who tested positive for SARS-CoV-2 between March 16 and April 25th, 2020. Data from electronic medical records were retrieved and compared between KTRs without AKI and KTRs with AKI. RESULTS: One pt was excluded due to DGF. Final analysis of AKI in KTRs with proven COVID-19 was done on 38 patients of which 30 were AA (79%). AKI occurred in 71.1% of COVID-19 KTRs (n=27), of whom 6 (22.2%) patients required HD. The incidence of AKI in our cohort was 71% (27/38). AKI rate among AA was 76.7% vs. 50% in non-AA cohort (p=0.195). In a univariate logistic regression analysis, AA race was not significantly associated with AKI OR (3.4, CI [0.68-17.4], p=0.14). After risk adjustment by race, patients with diabetes showed a significantly higher risk of AKI (adjusted OR 19.85 CI [1.65-58.66], p=0.012). KTRs with AKI had more preexisting RAAS inhibitor use than KTRs without AKI (P=0.03). CONCLUSIONS: KTRs infected with SARS-CoV-2 have a high incidence of AKI, with associated increased morbidity and mortality. Though no racial differences in mortality were noted in our KTRs with AKI, we await data from registries to help elucidate this difference.

Surgery

Wiseman A, Akalin E, Dadhania DM, DeMattos A, Doshi M, Friedewald J, Klein C, Leca N, Nicoll K, Pesavento T, Preczewski L, **Samaniego M**, Singh N, and Bloom R. Defining the Roles and Responsibilities of the Kidney Transplant Medical Director: A Necessary Step for Future Training, Mentoring, and Professional Development. *Am J Transplant* 2020; Epub ahead of print. PMID: 33021008. [Request Article](#)

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The management of a kidney transplant program has evolved significantly in the last decades to become a highly specialized, multidisciplinary standard of care for end stage kidney disease. Transplant center job descriptions have similarly morphed with increasing responsibilities to address a more complex patient mix, increasing medical and surgical therapeutic options, and increasing regulatory burden in the face of an ever-increasing organ shortage. Within this evolution, the role of the Kidney Transplant Medical Director (KTMD) has expanded beyond the basic requirements described in the United Network for Organ Sharing bylaws. Without a clear job description, transplant nephrology trainees may be inadequately trained and practicing transplant nephrologists may face opaque expectations for the roles and responsibilities of Medical Director. To address this gap and clarify the key areas in which the KTMD interfaces with the kidney transplant program, American Society of Transplantation (AST) formed a Task Force of 14 AST KTMDs to review and define the role of the KTMD in key aspects of administrative, regulatory, budgetary, and educational oversight of a kidney transplant program.

Urology

Hiller SC, Qi J, **Leavitt D**, Frontera JR, Jafri SM, Hollingsworth JM, Dauw CA, and Ghani KR. Uteroscopy in Patients Taking Anticoagulant or Antiplatelet Therapy: Practice Patterns and Outcomes in a Surgical Collaborative. *J Urol* 2020; Epub ahead of print. PMID: 33035142. [Full Text](#)

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PURPOSE: AUA guidelines recommend ureteroscopy (URS) as first-line therapy for patients on anticoagulant (AC) or antiplatelet (AP) therapy, and advocate using a ureteral access sheath (UAS). We examined practice patterns and unplanned healthcare utilization in these patients in Michigan. **MATERIALS AND METHODS:** Using the Michigan Urological Surgery Improvement Collaborative (MUSIC) clinical registry, we identified URS cases from 2016 to 2019. We assessed outcomes and adherence to guidelines based on therapy at time of URS: (1) AC: continuous warfarin or novel oral agent therapy, (2) AP: continuous clopidogrel or aspirin therapy, (3) Control: not on AC/AP therapy. We fit multivariate models to assess AC or AP therapy association with emergency department (ED) visits, hospitalization, and UAS use. **RESULTS:** In total, 9982 URS were performed across 31 practices, with 3.1% and 7.8% on AC and AP therapy, respectively. There was practice (0-21%) and surgeon (0-35%) variation in performing URS on AC/AP, regardless of volume. After adjusting for risk factors, AC or AP therapy was not associated with ED visits. Hospitalization rates in AC, AP, and control groups were 4.3%, 5.5%, and 3.2%, respectively, and significantly increased with AP therapy (OR 1.48, 95% CI: 1.02-2.14). Practice-level UAS use varied (23-100%), and was not associated with AC/AP therapy. Limitations include inability to risk stratify between type/dosage of AC/AP therapy. **CONCLUSIONS:** We found practice and surgeon-level variation in performing URS while on AC/AP therapy. URS on AC is safe, however AP therapy increases the risk of hospitalization. Despite guideline recommendations, UAS use is not associated with AC/AP therapy.

Conference Abstracts

Behavioral Health Services/Psychiatry

Imtiaz Memon R, Imran N, Aamer I, Imran Sharif M, Hassan Bodla Z, and Naveed S. 1.16 THE EFFECT OF QUARANTINE ON THE EMOTIONAL WELL-BEING OF KIDS: A SYSTEMATIC REVIEW. *Journal of the American Academy of Child and Adolescent Psychiatry* 2020; 59(10):S144.

Objectives: COVID-19 has a significant impact on the mental health of children and adolescents including adverse consequences from quarantine or isolation. In this systematic review, we explore the impact of quarantine and isolation on psychological well-being of youth and propose a comprehensive strategy to reduce psychological burden. **Methods:** Three electronic databases including PubMed, Scopus, and Web of Science were searched for relevant articles by using the following search terms: (stigma OR stigmas OR stigmatization OR stigmatization) AND (psych* OR mental OR anxiety OR depression OR stress OR insomnia OR adjustment) AND (quarantin* OR patient isolation OR isolate* OR lockdown OR lock-down OR cordon) AND (child* OR adolescent OR adolescence OR youth). Two independent reviewers performed title and abstract screening followed by full-text screening by using predetermined eligibility criteria. Data were extracted for study population, country of study, scales used to measure for outcome, summary of results, and limitations. **Results:** The initial search found 530 unique citations, and 10 studies were included after thorough screening. Among the included studies, the study design was cohort in 4 studies, cross-sectional in 3, and descriptive qualitative in 3. The most common diagnoses were acute stress disorder, adjustment disorder, grief, and PTSD. There was also evidence for restlessness, irritability, anxiety, clinginess, and inattention with increased screen time in children during quarantine. **Conclusions:** This review helps in improving the understanding of quarantine's effects on children and adolescents, such as mental health issues, stigma, physical health, education, socialization, and parental perception. We also propose interventions for quarantined children through education, information dissemination, behavioral activation, health care system response, school-based strategies, and other coping techniques. ADOL, PRE, WL

Cardiology/Cardiovascular Research

Al-Hijji M, Eleid M, **Wang DD**, Kodali S, Kaptzan T, El Sabbagh A, Oh J, **O'Neill W**, Rihal C, and Guerrero M. TCT CONNECT-347 Overexpansion of Balloon-Expandable Aortic Transcatheter Heart Valves in the Mitral Valve Position. *Journal of the American College of Cardiology* 2020; 76(17):B149-B150.

Background: Transcatheter mitral valve replacement using balloon-expandable aortic transcatheter heart valves (THVs) is emerging as alternative treatment for high surgical risk patients with symptomatic mitral valve disease due to bioprosthetic valve dysfunction, failed annuloplasty ring, and mitral annular calcification (MAC). THV deployment using higher contrast volume in the delivery balloon than nominal amount recommended by the manufacturer is not uncommon in order to flare the ventricular edge of the THV stent to help decrease embolization risk to the left atrium or treat paravalvular leak. This study aimed to determine the prevalence of THV overexpansion when used for mitral valve-in-valve, valve-in-ring, and valve-in-MAC, as well as its effects on rate of transvalvular mitral regurgitation (MR) and procedural outcomes. **Methods:** A subanalysis was performed on 91 patients who were enrolled in the multicenter MITRAL (Mitral Implantation of Transcatheter Valves) trial from February 2015 to December 2017. The cohort was divided into 3 groups (nominal expansion, <25% overexpansion, and ≥25% overexpansion) depending on the maximum amount of Edwards balloon filling during the procedure. The primary safety endpoint was a technical success. The primary performance endpoint was absence of MR grade ≥2+ or mitral valve gradient ≥10 mm Hg at 30 days and 1 year. **Results:** Mean age of patients was 74.5 ± 8.8 years and 52 were women (57.1%). Mean STS (Society of Thoracic Surgeons) score for 30-day mortality was 9.9 ± 6.6 for the entire population. Twenty-seven patients (29.7%) had THVs deployed at nominal expansion, whereas 64 THVs (70.3%) required overexpansion (53 required <25% overexpansion and 11 required ≥25% overexpansion). Technical success was achieved in 23 of 27 (85.2%) in nominal expansion group; 44 of 53 (83.0%) with <25% overexpansion, and 8 of 11 (72.7%) in ≥25% overexpansion group (p = 0.67). Thirty-day all-cause mortality was 8 of 91 (8.8%) for the entire cohort (mitral valve-in-valve: 3.3%, mitral valve-in-ring: 6.7%, and valve-in-MAC: 16.7%) without significant

difference according to degree of overexpansion. Paravalvular leak grade $\geq 2+$ was seen in 5 patients (nominal expansion: 1, $<25\%$ overexpansion: 2, $\geq 25\%$ overexpansion: 2) and only 1 patient had residual transvalvular MR grade $\geq 2+$ at end of transcatheter mitral valve replacement procedure (1 of 91, 1.1%). At 1 year, none of the 65 patients (71.4%) (nominal: 21, $<25\%$ overexpansion: 35, $\geq 25\%$ overexpansion: 9) who had echocardiographic follow-up had transvalvular MR grade $\geq 2+$. Conclusion: Overexpansion during transcatheter mitral valve replacement using balloon-expandable aortic THV to flare the ventricular edge of the THV stent frame was not associated with significant rate of transvalvular MR. Further studies are needed. Categories: STRUCTURAL: Valvular Disease: Mitral

Cardiology/Cardiovascular Research

Anderson M, **O'Neill W**, Ghu I, Ramzy D, and Kapur N. TCT CONNECT-185 Early Impella RP Support Improves Outcomes for Acute Right Ventricular Failure Complicated by Cardiogenic Shock. *Journal of the American College of Cardiology* 2020; 76(17):B79.

Background: The RECOVER RIGHT trials established the safety and efficacy of Impella RP for acute right ventricular failure (RVF) management. We now explored real-world performance of the Impella RP for RVF. Methods: This is a prospective, multicenter study of Impella RP support for RVF after durable left ventricular assist device (LVAD) implantation, acute myocardial infarction, or open cardiac surgery. We compared patients who would have met the RECOVER RIGHT trial enrollment criteria (RECOVER RIGHT–like group) to those who did not (salvage group). The primary endpoint was survival to 30 days after device explant or at hospital discharge (whichever was longer), or to induction of anesthesia to for durable LVAD or cardiac transplantation. Results: Sixty-six patients (mean age 65 ± 12 years, 71% male) were included. Patients received an average of 3.5 ± 1.4 inotropes and/or vasopressors and 53% had mechanical circulatory support pre-Impella. The salvage group had more hemodynamic instability and longer duration of shock pre-Impella RP. More patients in the RECOVER RIGHT–like group reached the primary endpoint than the salvage group (72.7% vs. 15.9%, $p < 0.001$). A ≥ 48 -h delay to Impella RP support was an independent predictor of mortality (relative risk: 1.65, 95% confidence interval: 1.19 to 2.3). [Formula presented] Conclusion: RECOVER RIGHT–like patients had higher survival than salvage patients, which may reflect shorter time from shock onset to initiation of Impella RP support. Early identification of patients requiring right-heart support may be critical to improve clinical outcomes for RVF. Categories: CORONARY: Hemodynamic Support and Cardiogenic Shock

Cardiology/Cardiovascular Research

Attar D, Lekura J, Kalus JS, Al-Darzi W, Williams CT, and Grafton GF. Impact of A Pharmacist-Led Heart Failure Clinic on Guideline-Directed Medical Therapy. *Journal of Cardiac Failure* 2020; 26(10):S129.

Introduction: ACE-I/ARBs, beta-blockers (BB), and aldosterone antagonists are standard of care for patients with heart failure and reduced ejection fraction (HFrEF). Studies have shown that a pharmacist-managed heart failure (HF) medication titration clinic increases the percentage of patients on optimal doses of ACE-I/ARB and BB. Pharmacists' role in improving follow-up, increasing access to HF medications, and impacting clinical outcomes is not well described in the literature. Hypothesis: Including pharmacists in a HF clinic for management of HFrEF leads to greater achievement of target doses of guideline-directed medical therapy (GDMT) within 3 months of an initial visit. Methods: This was a prospective, quasi-experimental study comparing patients with HFrEF seen in a pharmacist-run HF clinic to patients managed by usual care. Patients whose initial visit was between September 2019 and January 2020 were included. The primary endpoint was number of patients who reached target or maximally tolerated doses of GDMT within 3-months of the initial visit. Initial and follow up encounters occurred via face-to-face visits in both groups. Secondary endpoints included number of encounters, medication changes, time to follow-up post-discharge, and number of patients considered for ARNI. Results: Thirty-nine patients in the pharmacist group and 35 patients receiving usual care were included. Fifteen of the 39 patients were referred to a pharmacist during hospital admission. Within the pharmacist group, the median time to follow up post-discharge was 15 days (IQR, 10.5 - 21.5) with a pharmacist and 31 days (IQR, 24 - 41) with a cardiologist. Including those lost to follow up, GDMT at target doses was achieved in 23/39 in the pharmacist group versus 4/35 in the usual care group (59% vs 11.4 %; $P < 0.001$) (Table 1). Patients in the pharmacist group were seen more frequently and were more likely to receive HF

education, ARNI consideration, and medication changes over 3-months (Table 2). Conclusions: Pharmacist involvement in HFrEF management improves patient care with achievement of GDMT earlier than usual care and more frequent follow-up. Other benefits include HF education, greater consideration for ARNI, and earlier access to a healthcare provider after hospital discharge.

Cardiology/Cardiovascular Research

Basir M, Gorgis S, Lemor A, Ghiu I, Kelley R, McRae T, Khuddus M, Sharma R, Lim M, Nsair A, Wohns D, Mehra A, Lin L, Pinto D, Kapur N, and **O'Neill W.** TCT CONNECT-176 Diastolic Suction Alarms Are an Early Marker for Right Ventricular Failure in the Setting of Left Ventricular Mechanical Circulatory Support. *Journal of the American College of Cardiology* 2020; 76(17):B76.

Background: Right ventricular failure (RVF) is associated with worse outcomes in patients with acute myocardial infarction and cardiogenic shock (AMICS). Diastolic suction alarms may be an early marker for RVF. Methods: Patients enrolled in the National Cardiogenic Shock Initiative who underwent right heart catheterization demonstrating a central venous pressure (CVP) >12 mm Hg and in whom an Automated Impella Controller (AIC) log was available within the first 24 h of support were included. RVF was defined as a CVP >12 mm Hg with a pulmonary artery pulsatility index <1. Results: A total of 100 patients were included in the analysis. Patients with RVF (n = 48) were compared to those without RVF (n = 52). Patients with RVF were more likely to have active CPR at the time of Impella placement (20.8% vs. 4.0%, $p < 0.01$) and RCA involvement (54.2% vs. 27.3%, $p < 0.01$). Patients with RVF had lower MAP (46.4 vs. 54.6 mm Hg, $p = 0.02$) and higher lactate (7.1 vs. 4.5 mmol/l, $p = 0.03$) on admission. Patients with RVF had persistently higher lactate at 12 hours (5.6 vs. 3.4 mmol/l, $p = 0.04$). Patients with RVF had longer duration of diastolic suction (558 s vs. 210 s, $p = 0.02$), which was associated with higher in-hospital mortality (Figure). [Formula presented] Conclusion: Diastolic suction alarms are an early marker of RVF in patients with elevated filling pressures being treated with left-sided Impella support. Increased duration of diastolic suction is associated with worse outcomes. Categories: CORONARY: Hemodynamic Support and Cardiogenic Shock

Cardiology/Cardiovascular Research

Basir M, Taylor A, **Lemor A, Gorgis S,** Tehrani B, Truesdell A, Bharadwaj A, Kolski B, Gelormini J, Todd J, Lasorda D, Smith C, Riley R, Marso S, Federici R, and **O'Neill W.** TCT CONNECT-29 Vasopressors Have Independent Adverse Impact on Survival in Patients With Acute Myocardial Infarction Cardiogenic Shock. *Journal of the American College of Cardiology* 2020; 76(17):B13.

Background: Increasing doses of vasopressors are associated with increased mortality in patients presenting with acute myocardial infarction and cardiogenic shock (AMICS). A causal link to independent harm is confounded by the fact that higher levels of vasopressors may be related to decreasing intrinsic cardiac power output (CPO). Methods: The NCSI is a single-arm prospective trial using mechanical circulatory support (MCS) with Impella for patients with AMICS. Early initiation of MCS placement pre-percutaneous coronary intervention (PCI) and rapid de-escalation of vasopressors guided by systematic use of hemodynamic measures led to a 70% in-hospital survival rate for the first 300 patients enrolled from July 2016 to December 2019 in 57 sites. Because MCS can enhance CPO and decrease needs for vasopressors, we were able to assess the independent impact of increasing dosing of vasopressors on survival. Results: Hemodynamic measurements were obtained on patients immediately after MCS and PCI. Survival curves were constructed based on CPO and use of vasopressors (Figure). For patients with $CPO \leq 0.6$ W, survival rate was (77.3%, 45.0%, and 35.3%; $p = 0.02$) when 0, 1, or ≥ 2 inotropes were used, respectively. Similarly, for patients with $CPO \geq 0.6$ W, survival rate was (81.7%, 72.6%, and 56.8%; $p = 0.01$), respectively. Logistic regression analysis demonstrates that increasing requirements for inotropes were independently associated with an increase in mortality ($p = 0.02$). [Formula presented] Conclusion: Increasing requirements for vasopressors are associated with an increase in mortality in AMICS irrespective of underlying CPO. Methods to decrease need for vasopressors may enhance survival in AMICS. Categories: CORONARY: Hemodynamic Support and Cardiogenic Shock

Cardiology/Cardiovascular Research

Eng M, Abbas A, Hahn R, **Wang DD**, Eleid M, and **O'Neill W**. TCT CONNECT-150 Real World Outcomes With Small (20-mm) Balloon Expandable Sapien 3 Valves Compared to Larger Valves (23-, 26-, and 29-mm). *Journal of the American College of Cardiology* 2020; 76(17):B64.

Background: Small bioprosthetic valves have been associated with higher gradients and subsequently, patient prosthesis mismatch (PPM). We sought to compare the outcomes of patients undergoing implantation of Edwards SAPIEN 3 or SAPIEN 3 Ultra (ES3/U) 20-mm valves against those receiving >20-mm ES3/U valve prostheses (23-, 26-, and 29-mm) out to 1 year. Methods: All patients who underwent transfemoral transcatheter aortic valve replacement (TAVR) with ES3 or ES3U in stenotic native valves between June 2015 and Jan 2020 were included in the analysis. Baseline characteristics and outcomes for patients receiving 20-mm valves (n = 3,932) were compared to those receiving >20-mm S3/U valves (n = 128,798) after propensity matching. The 30-day and 1-year outcomes were based on Kaplan-Meier estimates and all comparisons were made using the log-rank test. Multivariable analysis determined independent predictors and association of post-TAVR hemodynamic parameters with 1-year all-cause mortality post-TAVR. All patients in the study cohorts were linked to the CMS claims database. Results: Patients receiving 20-mm valves were mainly female (96.4%) and had less vascular disease but more multivalvular disease compared to the patients receiving > 20-mm valves. Overall 30-day Society of Thoracic Surgeon score risk was higher in 20-mm patients (7.1% vs. 5.8%). Small valves in the propensity-matching analysis showed significantly higher discharge gradients (15.7 ± 7.09 mm Hg vs. 11.7 ± 5.54 mm Hg, p < 0.0001) and echo-derived severe PPM rates (21.5% vs. 9.7%, p < 0.0001). However, this difference did not impact 1-year all-cause mortality (20-mm: 13.0% vs. >20-mm: 12.7%, p = 0.72) or any of the other major adverse event rates and outcomes (i.e., cardiac death, stroke, major vascular complication, life-threatening bleeding, re-hospitalization, and quality of life) between the 2 cohorts. Based on a multivariable analysis post-TAVR, elevated echo gradient was associated with reduced mortality whereas the presence of severe-PPM was not associated with 1-year all-cause mortality. The presence of moderate/severe paravalvular leak at discharge was an independent predictor of 1-year mortality (hazard ratio: 1.82; 95% confidence interval: 1.41 to 2.34; p < 0.001). Conclusion: Small balloon expandable (20-mm) valves were associated with higher gradients and severe PPM rates compared to larger (>20-mm) valves, but these factors were not associated with significant differences in 1-year all-cause mortality or rehospitalization. Categories: STRUCTURAL: Valvular Disease: Aortic

Cardiology/Cardiovascular Research

Goldschmidt M, Mazimba S, Grayburn P, Hage A, Kourkovei P, **Cowger J**, Simmons L, Moe G, Mishkin J, Platts D, Gordon R, Ajello S, Marcoff L, and Toma M. Six-month and One-year Outcomes for Repair in Patients with Functional Mitral Regurgitation from the CLASP Study. *Journal of Cardiac Failure* 2020; 26(10):S8.

Background: Transcatheter mitral valve repair has emerged as a viable option for treating functional mitral regurgitation (FMR). We report results for the FMR cohort from the multicenter, prospective, single arm CLASP study with the PASCAL transcatheter valve repair system (Edwards Lifesciences, Irvine, CA). Methods: Eligible patients had clinically significant and symptomatic MR ≥3+ and were deemed candidates for transcatheter repair by the local heart team. The study outcomes were evaluated by an independent clinical events committee and echocardiographic core lab. The primary safety endpoint was a composite MAE rate at 30 days of cardiovascular mortality, stroke, MI, new need for renal replacement therapy, severe bleeding, and re-intervention for study device-related complications. Results: Of the 109 patients enrolled (intent to treat/ITT and roll-in), 73 (67%) had FMR as determined by the core lab. Mean age was 73 years, 55% male, 60% NYHA Class III/IV with 100% MR grade ≥3+. Successful implantation was achieved in 96% of patients. At 30 days, the MAE rate was 11.0% including one cardiovascular mortality, one stroke, and one conversion to mitral valve replacement surgery. At 30 days, 88% of patients were in NYHA Class I/II (p<0.001), MR grade was ≤1+ in 77% of patients and ≤2+ in 96% of patients. Improvements in 6MWD (+23 m, p=0.009) and KCCQ (+15 points, p<0.001) were observed. These outcomes were sustained at six-months. In addition, we report one-year follow up of the first 38 FMR patients (ITT): 89% one-year survival rate (KM estimate) with 80% freedom from HF hospitalization and no late strokes. At 1 year, MR grade was ≤1+ in 79% of patients and ≤2+ in 100% of patients. 83% of patients were in NYHA Class I/II (p<0.001), 6MWD improved by 24 m (p=0.261) and KCCQ improved by

13 points ($p=0.002$). Conclusions: This study demonstrates that the PASCAL repair system is safe and results in remarkable MR reduction in patients with FMR. 100% of patients achieved $MR \leq 2+$, and ~ 80% achieved $MR \leq 1+$, sustained at one year. Results show a high survival rate, low complications, and sustained improvements in functional status, exercise capacity, and quality of life at one year.

Cardiology/Cardiovascular Research

Hariri IM, Dardas T, Kanwar M, Cogswell R, Gosev I, Molina E, Myers SL, Kirklin JK, Shah P, Pagani FD, and **Cowger JA**. Longterm Survival on LVAD Support: Limitations Driven by Development of Device Complications and End-Organ Dysfunction. *Journal of Cardiac Failure* 2020; 26(10):S143-S144.

Introduction: Survival is nearly 50% after 5 years of LVAD support. While preop variables can predict short-term (ST) survival, correlates of long term (LT) survival remain poorly characterized. Hypothesis: We hypothesize that preop risk stratification will be limited to predicting ST survival and not LT success. Method: Patients ($n=16474$) undergoing LVAD implant (2012-18) in Intermacs-STS were grouped according to time on support: ST (<1 year, $n=4468$), mid-term (MT, 1-3 years, $n=8991$) and LT (≥ 3 years, $n=3015$). Separate multiphase hazard analyses were performed to identify correlates of LT survival in those alive and on LVAD support at 1 and 3 years (Ys). Results: Of those alive on LVAD support at 1 Y, the 3, 5, and 6 Y survivals were 75%, 53%, and 45%, respectively. Patients who were alive on LVAD support at 3 Ys had survivals of 60% at 6 Ys. The table shows adjusted associations between clinical variables and mortality for the MT and LT survival groups starting at 1 and 3 Ys, respectively. For the MT group, older, obese and Caucasian patients and those with preop RV dysfunction, active smoking, unmarried status or comorbidities had higher mortality after 1 Y of support. The occurrence of postop malnutrition, renal, and hepatic dysfunction also increased mortality. Finally, each episode of stroke, device infection or device malfunction increased mortality by 13-42%. For the LT group, postop organ dysfunction and malnutrition impacted extended LVAD survival and mortality increased by 10-46% per adverse event. The only preop correlates of survival beyond 3 Ys were older age, Caucasian race, and history of CABG. Conclusion: The success of LVAD support hinges on achieving LT survival. In operative survivors, LT LVAD survival is heavily constrained by the occurrence of events after LVAD placement. Preop, this also limits our ability to provide individualized, LT survival estimates.

Cardiology/Cardiovascular Research

Ijaz N, Taleb I, Kyriakopoulos CP, **Demetris Z**, **Peruri A**, Richins TJ, Dranow L, Tang D, **Nemeh H**, Stehlik J, Koliopoulou AG, Selzman CH, Alharethi R, **Cowger J**, Shah P, and Drakos SG. A Novel Risk Score Predicts Early Right Ventricular Failure after Lvad: A Derivation-validation Multicenter Study. *Journal of Cardiac Failure* 2020; 26(10):S149.

Introduction: Right ventricular failure (RVF) after LVAD implantation is associated with increased morbidity and mortality. Despite several RVF predictive models, poor performance in external validation cohorts has limited their widespread clinical adoption. Objective: To develop a novel RVF predictive model, ascertain its performance in an independent validation cohort, and develop an RVF risk score. Methods: Consecutive LVAD patients were prospectively enrolled at the Utah Transplantation Affiliated Hospitals (U.T.A.H) Cardiac Transplant Program ($n=477$, Derivation cohort). LVAD patients from Inova Heart & Vascular Institute and Henry Ford Medical Center formed the external dataset ($n=321$, Validation cohort). The primary outcome was early RVF, defined as the need for RVAD or intravenous inotropes for >14 days. The secondary outcome was 3-year all-cause mortality. Multivariable logistic regression analysis was used to develop a predictive model. An RVF risk score was developed using weighted points based on the β -regression coefficients of the multivariable predictors. Results: The study included 798 patients, with a mean age of 56y, 84% male, and 30% INTERMACS Profile 1-2. Compared to the derivation cohort, the validation cohort had a higher proportion of African-Americans (37% vs 7%; $p<0.01$), patients with a history of HTN (60% vs 49%; $p=0.002$), and bridging to durable LVAD with short-term MCS (16% vs 8%; $p<0.01$). The incidence of RVF in the derivation and validation cohorts was 16% and 36%, respectively. Multivariable analysis yielded 7 factors associated with RVF (African-American, history of HTN, INTERMACS profile 1-2, $Na <130$ meq/L, $BUN >35$ mg/dL, PA pulse pressure <36 mmHg and $RA/PCWP >0.5$). The model had a c-statistic of 0.73 ([95% CI:0.67-0.79]; $p<0.01$) and 0.71 ([95% CI: 0.65 - 0.77]; $p<0.01$) in the derivation and validation cohorts, respectively. A 10-point RVF risk score was developed (Table). The presence of RVF was associated with a higher 1-year (33% vs 12%; $p<0.01$) and

3-year (39% vs 19%; $p < 0.01$) mortality. Conclusion: We propose a novel scoring system to predict post-LVAD RVF, achieving high discriminative performance after being tested in distinct and highly heterogeneous populations. This simple predictive tool could impact patient selection and perioperative management of LVAD patients.

Cardiology/Cardiovascular Research

Isseh IN, Gorgis S, Dagher C, Sharma S, Basir MB, and Parikh S. Escalating Temporary Mechanical Circulatory Support In Worsening Cardiogenic Shock: Feasibility In Advanced Heart Failure Therapy Candidates. *Journal of Cardiac Failure* 2020; 26(10):S55.

Background: Temporary mechanical circulatory support (tMCS) can be used in cardiogenic shock (CS) as a bridge to advanced heart failure therapies (AHFT) (durable LVAD, cardiac transplantation). tMCS escalation in worsening CS has never been studied and prognostication in this cohort is needed, particularly in candidates for AHFT. We evaluated potential predictors of survival and outcomes of those that received AHFT. Methods: From 07/2016-07/2018 we identified patients with worsening CS shock requiring tMCS escalation. Worsening CS was defined as persistent hypotension; increasing doses of vasopressors/inotropes; worsening end-organ perfusion parameters; and/or worsening invasive hemodynamics. tMCS escalation was defined as adding/exchanging tMCS device to existing tMCS. Potential prognostic variables were evaluated in ROC curves. All statistical tests were performed with a two-sided p value=0.05. Results: 81 consecutive patients (61 ± 14 y, 73% m) had worsening CS shock requiring tMCS escalation. Devices used were IABP, Impella (2 5, CP, 5 0), ECMO and Tandem (TandemHeart, TandemLife, ProtekDuo). Survival to discharge was 32%. Etiology of shock was heterogeneous (33% AMI; 62% decompensated heart failure). 62% were transfers from outside hospitals. Utilization of a PA catheter pre-escalation was associated with improved survival compared to absence of a PA catheter (40% vs 18%, $p = 0.05$). ROC curves demonstrated prognostic thresholds associated with survival: age < 53 y (80% specificity) and pre-escalation cardiac power output (CPO) > 0.92 Watts (87% specificity). While prognostic thresholds associated with mortality were: age > 69 y (81% specificity), BMI > 35 kg/m² (81% specificity), pre-escalation cardiac power output (CPO) < 0.53 Watts (82% specificity), pre-escalation lactate > 3 mmol/L (81% specificity). AUC was greatest in post-escalation blood pressure indicating persistence of hypotension post-escalation (SBP < 85 mmHg; MAP < 67 mmHg) was associated with a dismal prognosis (specificity 92% for both for predicting mortality). 7 patients went on to receive AHFT (49 ± 13.4 y, 57% m) with a mean BMI 32 ± 11.4 kg/m². 6 received durable LVAD during index hospitalization, 4 of which survived. 4 underwent transplant in subsequent hospitalizations, all of which survived. Majority had decompensated heart failure as etiology of shock (NICM=5, ICM=1, AMI=1) and received tMCS escalation within 1 day ($n = 6$). All patients were classified as Stage D SCAI CS at the time of escalation and 5 received vasopressors/inotropes. Majority of patients had a PA catheter at time of escalation ($n = 6$). Overall survival was higher in the AHFT compared to those that did not receive AHFT ($n = 5$, 71% vs $n = 21$, 28.4%, $p = 0.03$). Conclusions: tMCS escalation in worsening CS incurs poor survival overall (32%). tMCS escalation is feasible in stabilizing patients with worsening CS that are candidates for AHFT.

Cardiology/Cardiovascular Research

Karacsonyi J, **Alaswad K**, Choi J, Khatri J, Jaffer FA, Poomipanit P, Forouzandeh F, Koutouzis M, Tsiafoutis I, Patel M, Mahmud E, Krestyaninov O, Jefferson B, Patel T, Shah A, Chandwaney R, Wollmuth J, Sheikh A, Yeh R, Tamez H, Jaber W, Samady H, Malik B, Potluri S, Uretsky B, Doing A, Dattilo P, Elbarouni B, Love M, Vemmou E, Nikolakopoulos I, Xenogiannis I, Rangan B, Garcia S, Ungi I, ElGuindy A, Goktekin O, Rafeh NA, and Brilakis E. TCT CONNECT-230 The Impact of Laser Use on the Outcomes of Balloon Uncrossable and Balloon Undilatable Chronic Total Occlusion Percutaneous Coronary Intervention. *Journal of the American College of Cardiology* 2020; 76(17):B101-B102.

Background: We sought to examine the impact of laser use on the outcomes of balloon uncrossable and balloon undilatable chronic total occlusions (CTO) undergoing percutaneous coronary intervention (PCI). Methods: The baseline clinical and angiographic characteristics and procedural outcomes of 4,845 CTO PCIs performed between 2012 and 2020 at 32 international centers were examined. Results: Of the 4,845 CTOs 752 (15.5%), there were balloon uncrossable or balloon undilatable that were included in the further analyses. Mean patient age was 66.9 ± 10 years and 83% were men, with 51% prevalence of

diabetes mellitus. Laser was used in 20.3% of the lesions. Compared with cases in which laser was not used, laser use was associated with longer occlusion length (33 [21, 50] vs. 25 [15, 40] mm, $p = 0.0004$) and in-stent restenotic lesions (41% vs. 20%, $p < 0.0001$). Laser use was associated with higher technical (91.5% vs. 83.1%, $p = 0.010$) and procedural (88.9% vs. 81.6%, $p = 0.033$) success rates and similar incidence of major cardiac adverse events (3.92% vs. 3.51%, $p = 0.805$). Laser use was also associated with longer procedural (169 [109, 231] vs. 130 [87, 199], $p < 0.0001$) and fluoroscopy time (64 [40, 94] vs. 50 [31, 81], $p = 0.003$). [Formula presented] Conclusion: In a contemporary, multicenter registry balloon uncrossable and balloon undilatable lesions represented 15.5% of the CTO PCIs. Laser was used in approximately one-fifth of these cases. Use of laser was associated with higher technical and procedural success and similar major complication rates. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Karacsonyi J, Stanberry L, Alaswad K, Krestyaninov O, Choi J, Rangan B, Nikolakopoulos I, Vemmou E, Ungi I, and Brilakis E. TCT CONNECT-229 Predicting Technical Success of Chronic Total Occlusion Percutaneous Coronary Intervention: Comparison of 3 Scores. *Journal of the American College of Cardiology* 2020; 76(17):B100-B101.

Background: Several scoring systems were developed to assess procedural difficulty: Japan chronic total occlusion (J-CTO) the Prospective Global Registry for the Study of CTO Intervention (PROGRESS-CTO) and the prior Coronary artery bypass graft surgery, Age, Stump anatomy, Tortuosity degree, Length of occlusion and Extent of calcification (EuroCTO CASTLE) score. We thought to compare 3 CTO percutaneous coronary intervention (PCI) scores for predicting technical success. Methods: We compared the three scores for predicting technical success in 3,757 CTO PCIs enrolled in the PROGRESS-CTO Registry between 2016 and 2020 at 30 centers. Results: The technical and procedural success rates were 84.9% and 82.7%, respectively. Major cardiac adverse events occurred in 1.73%. The mean scores were as follows: J-CTO: 2.40 ± 1.30 , PROGRESS-CTO: 1.28 ± 1.02 , and CASTLE: 2.05 ± 1.33 . All the 3 scores performed moderately well: in the score only model the J-CTO score showed the highest discriminatory capacity (area under the curve [AUC]: 0.77, 95% confidence interval [CI]: 0.75 to 0.79), followed by the CASTLE (AUC: 0.76, 95% CI: 0.69 to 0.73, $p = 0.05$ vs. J-CTO) and the PROGRESS-CTO score (AUC: 0.71, 95% CI: 0.74 to 0.78, $p < 0.001$ vs. J-CTO and CASTLE). The 3 scores had similar sensitivity and specificity, except for slightly lower specificity for PROGRESS score that contains only angiographic characteristics and includes the fewest variables. [Formula presented] Conclusion: The 3 scores perform moderately well in predicting the technical success of CTO PCI with the J-CTO score having the best overall performance. CTO PCI scores can be very useful for periprocedural planning and risk-benefit assessment in contemporary practice. Categories CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Lansky A, Grines C, Moses J, **O'Neill W**, Ekono M, and Gregory D. TCT CONNECT-181 A Propensity Matched Analysis of Impella Use From a Large-Scale Claims Data: Influence of Analytic Methodology on Clinical Outcomes. *Journal of the American College of Cardiology* 2020; 76(17):B77-B78.

Background: A recently published large-scale, real-world study using the Premier Healthcare database designed to describe trends, outcomes, and cost across U.S. hospitals showed that Impella use was associated with higher rates of adverse events compared to the intra-aortic balloon pump (IABP) in patients undergoing percutaneous coronary intervention (PCI). The purpose of this study was to assess the impact of methodology on outcomes and interpretation of results from the same dataset. Methods: The Premier Healthcare dataset was used to compare outcomes of patients undergoing PCI with Impella or IABP from 2004 to 2016. We used propensity score matching to overcome unadjusted confounders noted in the published analysis where $<10\%$ of the overall study population was treated with Impella and all patients were combined regardless of disease severity or indication. Results: A total of 47,043 patients were identified (IABP 42,376; Impella 4,667) at 531 hospitals. Unadjusted mortality was similar between groups. The 1:1 propensity score matching on the basis of 21 covariates including patient demographics and comorbidities resulted in balanced Impella and IABP cohorts with 3,609 subjects in each group. There was no observed increased risk of AKI (1.4% vs. 1.0%; $p = 0.1375$), stroke (3.2% vs. 2.8%; $p =$

0.3033), bleeding requiring transfusion (4.3% vs. 3.7%; $p = 0.1902$), or death (24.4% vs. 22.9%; $p = 0.1495$) between Impella and IABP during the index hospitalization. Conclusion: In contrast to a prior analysis from the same large claims dataset, using propensity matching as a methodologic approach to control for confounders, the risk of adverse clinical outcomes of patients undergoing Impella was not increased compared to IABP-assisted PCI. The interpretation of large claims data are subject to inherent methodological limitations. When conclusions can drastically impact patient care, these should be interpreted with caution especially in absence of clinical stratifications on the basis of procedural indication for hemodynamic support such as cardiogenic shock or acute myocardial infarction for PCI. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Lemor A, Hernandez G, Patel S, Basir M, Villablanca P, Alaswad K, and O'Neill W. TCT CONNECT-27 Impact of Prior Coronary Artery Bypass in Elderly Patients Presenting With Acute Myocardial Infarction. *Journal of the American College of Cardiology* 2020; 76(17):B12.

Background: Elderly patients presenting with acute myocardial infarction (AMI) have complex coronary anatomy in part due to prior coronary artery bypass (CABG) surgery, percutaneous coronary interventions (PCI), and calcific and valvular disease. Methods: Using the National Readmission Database from January 2016 to November 2017, we identified hospital admissions for AMI in patients ≥ 75 years of age and divided them based on a history of CABG. We evaluated in-hospital outcomes, 30-day mortality, 30-day readmission, and predictors of PCI among cohorts. Results: Of a total of 296,062 patients ≥ 75 years presenting with an AMI, 42,147 (14%) had history of prior CABG. The majority presented with a non-ST-segment elevation myocardial infarction (NSTEMI), and those with prior CABG had higher burden of comorbidities and were more commonly male. The in-hospital mortality rate was significantly lower in those with prior CABG (6.7% vs. 8.8%; aOR: 0.88; 95% confidence interval [CI]: 0.82 to 0.94). Medical therapy was more common in those with prior CABG and 30-day readmission rates were seen more frequently in those with prior CABG. Predictors of not undergoing PCI included prior PCI, female gender, older age groups, heart failure, dementia, malignancy, and higher number of comorbidities. [Formula presented] Conclusion: In elderly patients with AMI the presence of prior CABG was associated with lower odds of in-hospital and 30-day mortality, as well as lower complications rates, and a decreased use of invasive strategies (PCI, CABG, and MCS). However, 30-day major adverse cardiac event readmission was higher in those with prior CABG. Categories: CORONARY: Acute Myocardial Infarction

Cardiology/Cardiovascular Research

Michaels AT, Peterson E, Luzum J, Gui H, Pinto Y, Sabbah HN, Williams LK, Snider J, and Lanfear DE. Biomarker Guided Therapy For Heart Failure With Mid-Range EF. *Journal of Cardiac Failure* 2020; 26(10):S37.

Background: Heart failure (HF) with mid-range ejection fraction (HFmrEF, EF 40-49%) accounts for ~15% of HF patients and these are a heterogeneous group with a phenotypic character that reflects aspects of both preserved and reduced EF HF. There are no proven treatments for this group but identifying subsets of patients that will respond to conventional therapies such as beta blockers (BB) would be desirable. We hypothesized that HFmrEF patients with elevated Nt-proBNP or ST2 would have more favorable response to BB therapy. Methods: A prospective registry was conducted that enrolled 1760 HF patients who met Framingham HF criterion and who received care through our health system and insurance product. Participants donated blood for biomarker measurements at enrollment and their medication exposure was quantified over time using pharmacy claims data. The current study utilized all participants who had EF 40-49% and baseline biomarker measurement ($n=338$). The primary endpoint was all-cause mortality. Biomarker categories were dichotomized at Nt-BNP >1000 ng/L and ST2 ≥ 35 ng/mL. We quantified the HR for BB exposure overall and divided by biomarker level using Cox models adjusted for MAGGIC score and BB propensity score. Results: Vital status and Nt-BNP measurements were available for all 338 patients, while 279 had ST2 measured, and 201 had both markers (Table 1). For Nt-BNP, 200 (58%) had elevated levels while 143 (42%) had low values. BB use in patients with elevated Nt-BNP levels had a hazard ratio (HR) of 0.43 ($p=0.1$) compared to HR 0.97 ($p=0.97$) in the low Nt-BNP group. For ST2, 195 patients (70%) had levels <35 ng/mL while 84 (30%) had elevated levels. BB use in the elevated ST2 cohort had a HR 0.08 ($p=0.71$) vs. 0.62 ($p=0.72$) in the low ST2 group, a statistically

significant interaction. (p int= 0.089). Both low marker groups had very low event rates (3.5% and 3.1% 1 year death, respectively). The combination of the two markers together (either elevated vs. both low) identified an especially low risk group with 1.5% dying and predicted the BB benefit association; in the low marker group BB HR =0.99 (p >0.99) while in patients with either ST2 or Nt-BNP elevated the BB HR was 0.06 (p=0.03). Conclusions: In this observational study of HFmrEF patients, those with low ST2 and Nt-BNP have low risk of death and little benefit of BB therapy whereas among the approximately two-thirds of patients with either marker elevated a substantial BB benefit association was seen

Cardiology/Cardiovascular Research

Nikolakopoulos I, **Alaswad K**, Choi J, Khatri J, Yeh R, Krestyaninov O, Khelimskii D, Jaffer FA, Rafah NA, ElGuindy A, Goktekin O, Karpaliotis D, Poomipanit P, Vemmou E, Karacsonyi J, Rangan B, Garcia S, Banerjee S, Burke MN, and Brilakis E. TCT CONNECT-236 Percutaneous Coronary Intervention of Chronic Total Occlusions Involving a Bifurcation: Insights From the PROGRESS-CTO Registry. *Journal of the American College of Cardiology* 2020; 76(17):B104.

Background: The impact of bifurcations at the proximal or distal cap on the outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has received limited study. Methods: We analyzed the clinical, angiographic, and procedural data of 6,066 cases performed for patients between 2012 and 2020 in a global CTO PCI registry. We compared 4 groups according to bifurcation location: "proximal and distal cap," "proximal cap only," "distal cap only," and "no bifurcation." Results: The CTO involved a bifurcation in 67% cases, as follows: proximal cap (n = 2,006, 33%), distal cap (n = 815, 13%), or both caps (n = 1,268, 21%). Proximal and distal cap patients were more likely to have had prior myocardial infarction (52% vs. 45% vs. 42% vs. 44%, p < 0.001) or coronary artery bypass grafting (35% vs. 26% vs. 32% vs. 27%, p < 0.0001) when compared with proximal cap only, distal cap only, and no bifurcation groups, respectively. Proximal and distal cap cases had higher Japan-CTO (2.9 ± 1.1 vs. 2.5 ± 1.2 vs. 2.4 ± 1.3 vs. 2 ± 1.3, respectively; p < 0.0001) and greater use of the retrograde approach (47% vs. 40% vs. 30% vs. 20%, respectively; p < 0.0001). Technical success was significantly lower in the proximal and distal cap group (79% vs. 85% vs. 85% vs. 90%, respectively; p < 0.0001), with major adverse cardiovascular event rates being similar (2.3% vs. 2.3% vs. 1.6% vs. 1.3%, respectively; p = 0.06). Compared with no bifurcation, the presence of any bifurcation was associated with higher Japan-CTO score (2.6 ± 1.2 vs. 2 ± 1.3; p < 0.0001) and lower technical success (83% vs. 90%; p < 0.0001). [Formula presented] Conclusion: More than two-thirds of CTO PCIs involve a bifurcation, which is associated with lower technical success but similar risk for complications. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Raad M, Gorgis S, Dabbagh M, Parikh S, and Cowger J. Characteristics and Outcomes of Patients with Heart Failure Admitted with Covid-19 in a Cohort Study from Southeast Michigan. *Journal of Cardiac Failure* 2020; 26(10):S74.

Introduction: Cardiovascular comorbidities confer worse outcomes for patients with Coronavirus disease 2019 (COVID-19), but the impact of heart failure (HF) with preserved (HFpEF) and reduced (HFrEF) ejection fraction has not been well characterized. The aim herein is to examine outcomes in COVID-19 patients with and without HF. Methods: Patients (n = 437) consecutively admitted with COVID-19 were categorized according to the presence vs. absence of HF and subcategorized according to HFpEF and HFrEF (EF <50%). The primary outcome was inpatient mortality with independent correlates were identified with logistic regression. Secondary outcomes included acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), and need for mechanical ventilation. Results: The median cohort patient age was 68 (56-76) years, 43% (n = 189) were female, and 41% (n = 179) were Caucasian. HF was present in 29.7% (n = 130) of patients of which 43.8% (n = 57) had HFrEF and 56.2% (N = 73) had HFpEF. Patients with HF were more likely to be of older age and have more comorbidities. Overall inpatient mortality in the cohort was 12.3%. Compared to patients without HF (7.6%), patients with HFpEF (39.1%) and HFrEF (23.5%) had higher inpatient mortality (p<0.05) and were more likely to develop AKI, require mechanical ventilation, and have worse ARDS (figure 1). ACE/ARB and/or hydroxychloroquine were not associated with mortality (p >0.05) and there were no differences in inflammatory markers (ferritin, D-dimer, CRP, LDH). Independent predictors of inpatient mortality included: HFpEF (adjOR 2.55

(1.37-4.76)), age > 65 years (adjOR 3.00 (1.66-5.43), African American race (adjOR 1.82 (1.00-3.30)), Other race (adjOR 2.34 (1.02-5.37), $p = 0.043$), cerebrovascular disease (adjOR 3.07 (1.54-6.10), $p = 0.001$), and chronic hypoxic respiratory failure [adjOR 3.02 (1.19-7.62), $p = 0.019$], whereas HFpEF was not (adjOR 1.58 (0.77-3.23). Discussion: HF is prevalent in patients admitted with COVID-19. Patients with HFpEF had 2.6-fold higher mortality than those without HF and greater burdens of inpatient complications. Patients with HFpEF with COVID19 may warrant closer outpatient monitoring and a lower threshold for admission.

Cardiology/Cardiovascular Research

Shah T, Chou J, Grines C, Chieffo A, Bellumkonda L, Sugeng L, Ghiu I, Moses J, **O'Neill W**, and Lansky A. TCT CONNECT-184 Impact of Sex and Timing of Impella Support in Patients With Acute Myocardial Infarction Complicated by Cardiogenic Shock. *Journal of the American College of Cardiology* 2020; 76(17):B78-B79.

Background: Randomized controlled trials studying Impella (Abiomed, Danvers, Massachusetts) usage in patients with acute myocardial infarction complicated by cardiogenic shock (AMICS) are limited. Retrospective data from the catheter-based Ventricular Assist Device Registry has demonstrated that pre-percutaneous coronary intervention (PCI) implantation of the device in AMICS patients is associated with a significant mortality benefit (odds ratio [OR]: 0.49, $p = 0.04$). Whether this effect varies by sex remains understudied. Methods: In-hospital data was collected from all AMICS patients prospectively enrolled in the RECOVER III post market approval observational study of the Impella device from 2017 to 2019. Univariate logistic regression models were used to identify the effects of baseline and procedural characteristics on in-hospital mortality. Identified statistically significant predictors and sex were included in the final multivariate logistic regression model. Results: Data were available for 82 females (41 with pre-PCI Impella vs. 41 with post-PCI Impella) and 266 males (167 pre-PCI vs. 99 post-PCI). Females had a survival benefit with Impella implantation pre-PCI compared to post-PCI (59% vs. 34%, $p = 0.03$); males did not (56% vs. 50%, $p = 0.40$). Survival for patients on 0, 1 to 2, or >2 inotropes pre-Impella was 71%, 43%, and 19% for females ($p = 0.001$) and 64%, 54%, and 31% for males ($p = 0.004$), respectively. The multivariate regression found that the following were significant independent predictors of in-hospital mortality: pre-PCI Impella implantation (OR: 0.516, $p = 0.03$), previously diagnosed renal insufficiency (OR: 2.482, $p = 0.02$), heart rate (OR: 1.013, $p = 0.03$), and systolic blood pressure (OR: 1.013, $p = 0.03$). However, sex was not an independent predictor ($p = 0.59$) and there was not a significant interaction between sex and pre-PCI Impella usage ($p = 0.13$). Conclusion: Early implantation of Impella provides a significant survival benefit, particularly to females. Sex discrepancies appear to be the result of differing baseline and hemodynamic characteristics at presentation. Taking these factors into consideration may help identify patients most likely to benefit from Impella support. Categories: CORONARY: Hemodynamic Support and Cardiogenic Shock

Cardiology/Cardiovascular Research

Singh H, Mehta R, **O'Neill W**, Lalonde T, Ghiu I, Chen-Hsing Y, Dutcheshen K, Schreiber T, and Rosman H. TCT CONNECT-172 Clinical Features and Outcomes of Acute Myocardial Infarction and Cardiogenic Shock Patients Treated With Impella: Early Compared With Recent Experience. *Journal of the American College of Cardiology* 2020; 76(17):B74.

Background: The percutaneous ventricular assist device, Impella (Abiomed, Danvers, Massachusetts), received U.S. Food and Drug Administration pre-market approval (PMA) for treatment of patients with acute myocardial infarction and cardiogenic shock (AMICS) on April 7, 2016. The purpose was to compare the clinical features and outcomes of early (pre-PMA) versus recent (post-PMA) Impella use in AMICS. Methods: We performed a retrospective analysis on 649 AMICS patients (291 early (December 20, 2008, to June 23, 2014) and 358 recent (January 8, 2017, to August 29, 2019) enrolled in catheter-based ventricular assist devices registry treated with Impella either before or after percutaneous coronary intervention (PCI). The primary endpoint was risk adjusted in-hospital mortality. Results: Mean age of patients was similar in early versus recent periods (65 ± 12 and 64 ± 11 years, respectively). The prevalence of hypertension, smoking, stroke, and New York Heart Association functional class III/IV CHF were higher and anoxic brain injury lower in recent group. Recent cohort also had more invasive hemodynamic monitoring and lesser use of intra-aortic balloon pump. The time to Impella from shock

onset was shorter and duration of support longer in recent patients who were also more likely to have the device implanted pre-PCI. Incidence of peri-PCI AKI, major bleeding or vascular complications were lower in the recent cohort. Observed in-hospital mortality was also lower in recent group (48% vs. 56%, $p = 0.043$) and showed similar trends favoring recent group for all subgroups examined. This difference was significantly attenuated after risk adjustment (adjusted odds ratio: 0.89; 95% confidence interval: 0.59 to 1.34; $p = 0.59$). Conclusion: The use of Impella in recent years was associated with lower observed in-hospital mortality that was mostly related to patients' comorbid conditions suggesting better selection in addition to changes in processes of care of these patients. In-depth understanding of the factors associated with lower mortality has the potential to improve outcomes of AMICS patients receiving Impella in community at large. Categories: CORONARY: Hemodynamic Support and Cardiogenic Shock

Cardiology/Cardiovascular Research

Smith R, Szerlip M, Lim S, Makkar R, Kar S, Kipperman R, Spargias K, **O'Neill W**, Ng M, Fam N, Rinaldi M, Raffel O, Walters D, Levisay J, Montorfano M, Latib A, Cohen G, Schäfer U, Marcoff L, and Webb J. TCT CONNECT-5 Six-Month and One-Year Outcomes for Transcatheter Repair in Patients With Mitral Regurgitation From the CLASP Study. *Journal of the American College of Cardiology* 2020; 76(17):B3.

Background: Transcatheter mitral valve repair has emerged as a viable option for treating mitral regurgitation (MR). We report results from the multicenter, prospective, single-arm CLASP study with the PASCAL transcatheter valve repair system (Edwards Lifesciences, Irvine, California). Methods: 109 intent to treat and roll-in patients with clinically significant MR $\geq 3+$ and deemed candidates for transcatheter repair by the local heart team were treated in the CLASP study. The study outcomes were evaluated by an independent clinical events committee and echocardiographic core laboratory. The primary safety endpoint was a composite MAE rate at 30 days of cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding, and re-intervention for study device-related complications. Results: Mean age was 76 years, 54% male, 57% New York Heart Association (NYHA) functional class III/IV, 100% MR grade $\geq 3+$ with 67% functional, 33% degenerative etiology. Successful implantation was achieved in 95% of patients. At 30 days, the MAE rate was 8.3% including 1 cardiovascular mortality, 1 stroke, and 1 conversion to mitral valve replacement surgery. 88% of patients were in NYHA functional class I/II ($p < 0.001$); MR grade was $\leq 1+$ in 80% of patients and $\leq 2+$ in 96% of patients. Significant improvements in 6-minute walk distance (+28 m; $p < 0.001$) and KCCQ (+16 points; $p < 0.001$) were observed. These outcomes were sustained at 6 months. We report 1-year follow-up of the first 62 intent to treat patients: 92% 1-year survival rate (KM estimate), no stroke, no late reintervention, and one late myocardial infarction. MR grade was $\leq 1+$ in 82% of patients and $\leq 2+$ in 100% of patients. 88% of patients were in NYHA functional class I/II ($p < 0.001$), 6-minute walk distance improved by 21 m ($p = 0.124$), and KCCQ improved by 14 points ($p < 0.001$). Conclusion: This study demonstrates the PASCAL transcatheter valve repair system is safe and resulted in significant MR reduction at 30 days and 6 months and was sustained at 1 year with 100% of patients achieving MR $\leq 2+$ and 82% MR $\leq 1+$. Results show a high survival and low complication rates with sustained improvements in functional status, exercise capacity, and quality of life at 1 year. Categories: STRUCTURAL: Valvular Disease: Mitral

Cardiology/Cardiovascular Research

Vemmou E, **Alaswad K**, Patel M, Mahmud E, Choi J, Jaffer FA, Doing A, Karmpalitotis D, Krestyaninov O, Khelinskii D, Nikolakopoulos I, Karacsonyi J, Xenogiannis I, Garcia S, Burke MN, Rafah NA, ElGuindy A, Goktekin O, Abdo A, Rangan B, and Brilakis E. TCT CONNECT-228 In-hospital Outcomes of CTO PCI in Octogenarians and Nonagenarians: Insights From the PROGRESS-CTO Registry. *Journal of the American College of Cardiology* 2020; 76(17):B100.

Background: The outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) in octogenarians and nonagenarians have received limited study. Methods: We compared in-hospital outcomes of CTO PCI between patients ≥ 80 years and < 80 -years-old in 6,233 CTO PCIs performed in 6,050 patients between 2012 and 2020 at 33 U.S. and international centers. Results: There were 415 octogenarians and nonagenarians in our study (7% of the total population). Compared with younger patients, octogenarians and nonagenarians were less likely to be men (73% vs. 83.2%, $p < 0.0001$) and more likely to have atrial fibrillation (27% vs. 12%, $p < 0.0001$) and prior coronary artery bypass graft surgery (43% vs. 29%, $p < 0.0001$). They were more likely to have CTOs with moderate/severe

calcification (71% vs. 46%, $p < 0.0001$), but had similar mean J-CTO scores (2.5 ± 1.3 vs. 2.4 ± 1.3 , $p = 0.09$). The most common crossing strategy used was antegrade wire escalation in both groups (84% in octogenarians/nonagenarians vs. 85% in younger patients, $p = 0.64$). Non-CTOs were treated at the same time in 32% of patients in the ≥ 80 -year-old group compared with 25% in the < 80 -year-old group ($p = 0.018$). Octogenarians and nonagenarians were more likely to have balloon uncrossable (17% vs. 10%, $p = 0.0006$) and balloon undilatable lesions (15% vs. 9%, $p = 0.006$). The octogenarians/nonagenarians had lower technical and procedural success (82.2% vs. 86.3%, $p = 0.02$, 80.3% vs. 84.8%, $p = 0.016$, respectively) and higher incidence of in-hospital major adverse cardiovascular events (MACE) (3.4% vs. 1.8%, $p = 0.02$) (Figure 1). Most in-hospital MACE events were cardiac tamponade requiring pericardiocentesis (Figure 2). [Formula presented] [Formula presented] Conclusion: CTO-PCI is feasible in octogenarians and nonagenarians, although success rates are lower, and the risk of complications is higher compared with younger patients. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Vemmou E, Quadros A, Dens J, Agostoni P, **Alaswad K**, Belli K, Carlino M, Karpaliotis D, Khelinskii D, Knaapen P, Krestyaninov O, Ojeda S, Padilla L, Pan M, Piccaro de Oliveira P, Rinfret S, Spratt J, Walsh S, Karacsonyi J, Nikolakopoulos I, Rangan B, Brilakis E, and Azzalini L. TCT CONNECT-240 CTO PCI for In-Stent Restenosis: Insights From a Pooled Analysis of Four Multicenter Registries. *Journal of the American College of Cardiology* 2020; 76(17):B106.

Background: The outcomes of percutaneous coronary intervention (PCI) for in-stent chronic total occlusions (CTOs) have received limited study. Methods: We examined the clinical, angiographic characteristics and procedural outcomes of 11,966 CTO PCIs performed at 11,756 patients at 108 U.S. and international centers between 2012 and 2020, pooling patient-level data from four multicenter registries. In-hospital major adverse cardiovascular events included death, myocardial infarction, stroke, and tamponade. Results: In-stent CTOs represented 15% of the total procedures ($n = 1,753$). Patients with in-stent CTOs had higher rates of diabetes mellitus (44% vs. 38%, $p < 0.0001$) and prior coronary artery bypass grafts (26.5% vs. 24%, $p = 0.0273$). In-stent CTOs had a higher Japan-CTO score (2.3 ± 1.3 vs. 2.2 ± 1.3 , $p = 0.009$) and less proximal cap ambiguity compared with de novo lesions (27% vs. 36%, $p < 0.0001$). Regarding successful crossing strategies, antegrade wiring was the most used strategy in the in-stent group (70% vs. 61%) followed by antegrade dissection/re-entry (17% vs. 21%) and retrograde crossing (13% vs. 18%, $p < 0.0001$). Intravascular imaging was used more often (43% vs. 35%, $p < 0.0001$) in the in-stent CTO group. Compared with de novo CTOs, in-stent CTO PCIs required less contrast (215 [150, 300] vs. 250 [180, 341] ml, $p < 0.0001$). Technical (85% vs. 85%, $p = 0.87$) and procedural (84% vs. 84%, $p = 0.82$) success rates were similar between in-stent and de novo CTOs as was the incidence of in-hospital major adverse cardiovascular events (1.7% vs. 2.2%, $p = 0.25$) (Figure). [Formula presented] Conclusion: In-stent CTOs represent 15% of all CTO PCIs and can be re-canalized with similar success and in-hospital complication rates as de novo CTOs. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Whitehead EH, Thayer K, Burkhoff D, Uriel N, Ohman EM, **O'Neill W**, and Kapur NK. Elevated Central Venous Pressure As A Trigger For Right Heart Failure Evaluation In Patients Receiving Left-sided Mechanical Support For Cardiogenic Shock. *Journal of Cardiac Failure* 2020; 26(10):S55.

Right ventricular failure (RVF) is associated with increased mortality among patients receiving left ventricular mechanical circulatory support (LV-MCS) for cardiogenic shock and requires prompt recognition and management. Increased central venous pressure (CVP) is an indicator of potential RVF. We analyzed the association between hemodynamic parameters and clinical outcomes among 132 patients with cardiogenic shock due to acute myocardial infarction in the cVAD registry who had a CVP measured during left-sided Impella support. CVP was significantly higher among patients who died in the hospital (14.0 vs 11.7 mmHg, $p=0.014$), and a CVP > 12 identified patients at significantly higher risk for in-hospital mortality (65% vs 45%, $p=0.02$). CVP remained significantly associated with in-hospital mortality even after adjustment in a multivariable model (adjusted OR 1.10 [95% CI 1.02-1.18] per 1 mmHg increase). LV-MCS suction events were non-significantly more frequent among patients with high

versus low CVP (62.11 vs 7.14 events, $p=0.067$). CVP is a single, readily accessible hemodynamic parameter which predicts a higher rate of short-term mortality and may identify sub-clinical RVF in patients receiving LV-MCS for cardiogenic shock.

Center for Individualized and Genomic Medicine Research

Michaels AT, Peterson E, Luzum J, Gui H, Pinto Y, Sabbah HN, Williams LK, Snider J, and Lanfear DE. Biomarker Guided Therapy For Heart Failure With Mid-Range EF. *Journal of Cardiac Failure* 2020; 26(10):S37.

Background: Heart failure (HF) with mid-range ejection fraction (HFmrEF, EF 40-49%) accounts for ~15% of HF patients and these are a heterogeneous group with a phenotypic character that reflects aspects of both preserved and reduced EF HF. There are no proven treatments for this group but identifying subsets of patients that will respond to conventional therapies such as beta blockers (BB) would be desirable. We hypothesized that HFmrEF patients with elevated Nt-proBNP or ST2 would have more favorable response to BB therapy. Methods: A prospective registry was conducted that enrolled 1760 HF patients who met Framingham HF criterion and who received care through our health system and insurance product. Participants donated blood for biomarker measurements at enrollment and their medication exposure was quantified over time using pharmacy claims data. The current study utilized all participants who had EF 40-49% and baseline biomarker measurement ($n=338$). The primary endpoint was all-cause mortality. Biomarker categories were dichotomized at Nt-BNP $>1000\text{ng/L}$ and ST2 $\geq 35\text{ng/mL}$. We quantified the HR for BB exposure overall and divided by biomarker level using Cox models adjusted for MAGGIC score and BB propensity score. Results: Vital status and Nt-BNP measurements were available for all 338 patients, while 279 had ST2 measured, and 201 had both markers (Table 1). For Nt-BNP, 200 (58%) had elevated levels while 143 (42%) had low values. BB use in patients with elevated Nt-BNP levels had a hazard ratio (HR) of 0.43 ($p=0.1$) compared to HR 0.97 ($p=0.97$) in the low Nt-BNP group. For ST2, 195 patients (70%) had levels $<35\text{ ng/mL}$ while 84 (30%) had elevated levels. BB use in the elevated ST2 cohort had a HR 0.08 ($p=0.71$) vs. 0.62 ($p=0.72$) in the low ST2 group, a statistically significant interaction. ($p_{\text{int}}=0.089$). Both low marker groups had very low event rates (3.5% and 3.1% 1 year death, respectively). The combination of the two markers together (either elevated vs. both low) identified an especially low risk group with 1.5% dying and predicted the BB benefit association; in the low marker group BB HR =0.99 ($p>0.99$) while in patients with either ST2 or Nt-BNP elevated the BB HR was 0.06 ($p=0.03$). Conclusions: In this observational study of HFmrEF patients, those with low ST2 and Nt-BNP have low risk of death and little benefit of BB therapy whereas among the approximately two-thirds of patients with either marker elevated a substantial BB benefit association was seen

Dermatology

Luther CA, Griffith JL, Kurland E, Al Shabeeb R, Eleryan M, Redbord K, and Ozog DM. The infection rate of intralesional triamcinolone and the safety of compounding in dermatology for intradermal and subcutaneous injection: A retrospective medical record review. *Journal of the American Academy of Dermatology* 2020; 83(4):1044-1048.

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Background: Intralesional injection of sterile medications remains a mainstay in dermatology, enabling a tailored, low-cost, in-office therapy. After the 2012 United States outbreak of fungal meningitis from contaminated intrathecally administered corticosteroids, there has been increased regulation of in-office compounding, regardless of the administration route. Studies demonstrating the safety data of in-office corticosteroid compounding for intradermal or subcutaneous use are lacking. Objective: To assess the incidence of infection caused by compounded in-office intralesional triamcinolone. Methods: A retrospective medical record review identified patients who received in-office intralesional corticosteroid injections in 2016. Medical documentation within 30 days of injection was reviewed for suspected infection. Results: The records of 4370 intralesional triamcinolone injections were assessed, of which 2780 (64%) were compounded triamcinolone with bacteriostatic saline. We identified 11 (0.25%) suspected localized infections, with 4 of the 11 in the compounding cohort. Of these, 7 of 11 occurred after injection of an "inflamed cyst." No hospitalizations or deaths occurred. No temporal or locational relationships were identified. Limitations: This study was limited to 2 academic institutions. A 30-day

postinjection time frame was used. Conclusion: In-office compounding for intralesional dermal and subcutaneous administration is safe when sterile products are used by medical practitioners. There is no increased risk of compounded triamcinolone relative to noncompounded triamcinolone.

Dermatology

Schaff E, Bergman D, Burmeister C, McHargue C, Lim H, and Siddiqui F. Impact of Gender and Race on Outcomes of Patients Treated for Mycosis Fungoides with Total Skin Electron Beam Therapy. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E47.

Background: Race and gender have been shown to affect patient outcomes in many different types of cancer. However, there is just one other paper which explores this in mycosis fungoides. Our institution is well suited for studying these disparities due to our diverse patient population. Objectives: To determine the impact of patient characteristics such as race and gender on the survival outcomes of patients with mycosis fungoides who have undergone total skin electron beam therapy as part of their treatment regimen. Methods: After IRB approval, 25 patients with mycosis fungoides who have undergone 26 courses of total skin electron beam therapy (TSEBT) were included in this analysis (one patient with 2 courses of TSEBT). These patients were treated between 2010 and 2019 with 36 Gy in 24 fractions over 8 weeks using the Stanford 6 technique. Data points were collected from all available medical records. Patients were stratified by race and by gender. Results: Patients were evenly distributed, with 13/25 African American (AA) vs 12/25 Caucasian, and 10/25 female vs 15/25 male. With a median follow up of 17 months (range 1-67 months), the progression free survival (PFS) at 6 months in African Americans vs Caucasians was 22% vs 39% ($p=0.25$) and at 1 year it was 7% vs 20% ($p=0.18$). When comparing by gender, the 6 month PFS for female vs male was 27% vs 33% ($p=0.95$) and at 1 year was 16% vs 11% ($p=0.96$). Overall survival (OS) at 1 year in AA vs Caucasians was 100% vs 73% ($p=N/A$) and at 2 years it was 71% vs 62% ($p=0.55$). When comparing by gender, the 1 year OS for female vs male was 89% vs 80% ($p=0.52$) and at 2 years it was 78% vs 53% ($p=0.35$). There were no significant differences in age, diagnosis to treatment time, previous treatment, or previous radiation therapy between the groups when comparing by race or by gender. Conclusions: To date there has been only one other paper addressing the factors of race and gender on the outcomes of TSEBT, and this paper had a relatively low percentage of AA patients (22%). In our study where the representation of AA patients is 52%, we confirmed that there is no significant difference in survival outcomes based on the patient's race. This was similarly observed in the comparison by gender as well. A major limitation of this study was the small sample size, as well as the retrospective nature of the analysis. Significantly, this study reinforces the point that in patients with Mycosis Fungoides, progression is almost inevitable and a multidisciplinary approach is the only effective means of management.

Diagnostic Radiology

Feldman A, Devpura S, Movsas B, Chetty I, Cook A, Rusu S, Brown S, Kim J, Sun Z, Ajlouni M, mayyas E, Liu J, Liu C, and Snell D. A Prospective Analysis of Quality of Life Data and Clinical Toxicity as a Function of Radiation Dose and Volume in Stage I Lung Cancer Patients after SBRT. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E64.

Background: Stereotactic body radiation therapy (SBRT) is an appropriate treatment option for patients with stage I non-small cell lung cancer (NSCLC) who are not surgical candidates. As these patients often present with significant co-morbidities, quality of life (QOL) outcomes are especially important. Objectives: To use a validated patient reported quality of life (QOL) assessment tool to measure clinical toxicity and patient reported quality of life (QOL) outcomes up to 36 months after SBRT in stage I NSCLC patients based on pre-treatment dosimetric parameters and tumor volumes. Methods: Fifty-six stage I NSCLC patients treated with SBRT (12 Gy x 4) were prospectively monitored for symptoms including cough, dyspnea, fatigue, and pneumonitis. Symptoms were measured at baseline (before treatment), immediately after treatment and 3, 6, 12, 18, 24, and 36 months post-treatment. Toxicity was graded from zero to five following the Charlson comorbidity and toxicity index. Quality of life was determined using the previously-validated Functional Assessment of Cancer Therapy-Trial Outcome Index (FACT-TOI) Lung questionnaire which incorporated three subscale endpoints: lung subscale (LSC), physical well-being (PWB) and functional well-being (FWB). Dosimetric parameters, including the mean lung radiation dose (MLD), and the volume of normal lung receiving at least 5, 10, 13 or 20 Gy (V5, V10, V13, and V20) were

obtained from the treatment plan. Pearson correlation and student t-test analyses were used to measure correlations and distinguish between lung metrics with QOL and clinical toxicities. Results: SBRT produced minimal toxicities. QOL (TOI, LSC, PWB, or FWB) at 3, 6, 12 and 24 months post-treatment were significantly correlated with V5, V10, V13, V20, or MLD. Radiation pneumonitis showed mild positive but statistically significant ($P < 0.05$) correlation with V20. Moreover, FWB at 3 months showed mild negative correlation with dyspnea. Conclusions: Lung SBRT treatment for patients with NSCLC, using a 12 Gy x 4 dose regimen, was well tolerated with minimal toxicity observed. A validated patient related quality of life assessment tool was used to identify the dosimetric parameters most crucial for treatment planning. Further follow-up is recommended.

Diagnostic Radiology

Wen N, Dai Z, Carver E, Liang E, Snyder J, Griffith B, and Movsas B. Glioblastoma MR Images Synthesis with Generative Adversarial Network. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E28.

Background: Automatic delineation of Glioblastoma (GBM) plays an important role in radiation therapy. Recently, segmentation algorithms using supervised deep neural networks (DNN) have shown promising results, but small volumes of annotated data pose challenges on powering them. Current collection of dataset relies on radiologists' contour as ground truth and is expensive and time-consuming. Objectives: One possible solution to overcome the limitation of small dataset is to generate synthetic MR images representing different clinical scenario. The aim of this study is to apply a generative adversarial network (GAN) to synthesize highly realistic MR images from manipulated annotations that are able to feed as new training samples for DNNs. Methods: Data was obtained from the BraTS multimodal Brain Tumor Segmentation Challenge 2018. 19 different institutions provided a total of 210 patients. T1WI, T1CE, T2WI, and FLAIR were provided for each patient. 82 patients were used for training and 128 patients for validation. The network consisted of a generator and two discriminators. Image per-pixel loss, perceptual loss and adversarial loss were used. By manipulating on annotations from radiologists, the generator was able to output new synthetic MR images, and boost the size of dataset. The realism of synthetic images was evaluated both quantitatively and qualitatively. Results: Synthetic image generated from non-manipulated annotation was compared with its corresponding real image. Mean Square Error (MSE), Mean Absolute Error (MAE), Peak Signal to Noise Ratio (PSNR), and Structural Similarity Index (SSIM) for synthetic MR images were 19.246 ± 0.308 , 23.375 ± 0.586 , 43.068 ± 0.443 and 0.788 ± 0.002 ; 19.249 ± 0.274 , 22.805 ± 0.583 , 43.054 ± 0.437 and 0.789 ± 0.004 ; 19.246 ± 0.290 , 23.391 ± 0.400 , 43.102 ± 0.45 and 0.784 ± 0.003 ; 18.930 ± 0.40 , 24.119 ± 1.48 , 43.126 ± 0.46 and 0.794 ± 0.005 , respectively, for T1, T1CE, T2 and Flair. A subset of 9 real and 10 generated patients were assessed by a physician. 8.3%, 41.7%, 50% of real images and 22.5%, 47.5%, 30% of synthetic images were commented as poor, marginal and good quality. The misclassified rate were 26.3%, 10.5%, 26.3% and 26.3% for T1, T1CE, T2 and Flair. Conclusions: We proposed to apply GAN to synthesize GBM MR images from manipulated annotations to increase the dataset size to train deep learning segmentation models. The evaluation results showed synthetic MRIs had comparable image quality to real MRIs that had potential to be used for DNN training.

Diagnostic Radiology

Zong W, Lee J, Pantelic M, and Wen N. Prediction of Gleason Grade Group of Prostate Cancer on Multiparametric MRI using Deep Machine Learning Models. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E9-E10.

Background: The Gleason Grade (GG) Group system has been introduced recently for more accurate stratification of prostate cancer (PCa). The grading system is based on the histologic patterns which is accessed from needle core biopsy, therefore it could be negatively impacted by the intratumor heterogeneity. Objectives: We aim to develop a deep learning algorithm to predict GG groups using multiparametric magnetic resonance images (mp-MRI). Methods: We studied a retrospective collection of 201 patients with 320 lesions from the SPIE-AAPM-NCI PROSTATEx Challenge (<https://doi.org/10.7937/K9TClA.2017.MURS5CL>), among which 98 patients with 110 lesions with GG available from biopsy. And the number of lesions in each subgroup was 36, 39, 20, 8, and 7, respectively, for GG 1-5. The images were acquired on two different types of Siemens 3T MR scanners. T2W images

were acquired using a turbo spin echo sequence and had a resolution of around 0.5 mm in plane and a slice thickness of 3.6 mm. The DWI series were acquired with a single-shot echo planar imaging sequence with a resolution of 2 mm in-plane and 3.6 mm slice thickness and with diffusion-encoding gradients in three directions. Three b-values were acquired (50, 400, and 800 s/mm²), and subsequently, the ADC map was calculated by the scanner software. Image pre-processing included registration and normalization. Image rotation and scaling were also used to increase the sample size and re-balance the number of lesions in various GG. To prevent over-fitting on a small sample size, we implemented a transfer learning model by carrying over the features learned from the malignancy classification of 320 lesions from our previous model into the GG prediction. And we replaced the end-to-end convolutional neural network (CNN) training model with a combination of feature extraction using CNN and classification using weighted extreme learning machine (wELM). Results: Features from the best performing model were extracted to represent each lesion, and those from the last convolutional layer were found constantly better than from all other layers. Based on 3-fold cross validation, the average validation results for sensitivity, specificity, positive predictive value, and negative predictive value for differentiation of each GG (1-5) were (1, 0.99, 0.97, 1), (0.69, 0.85, 0.73, 0.83), (0.9, 0.69, 0.46, 0.97), (0.89, 0.64, 0.16, 0.99), and (1, 0.78, 0.39, 1), respectively. GG4 had the highest false positive values. GG 3 was often misclassified as GG 4. Results of GG3-5 vs. GG1-2 were (0.82, 0.87, 0.76, 0.92). The stratification of GG4-5 vs. GG1-3 was (0.87, 0.81, 0.42, 0.98). Conclusions: This work has made substantial progress tackling the challenging task of GG prediction from mp-MRI due to a smaller and unbalanced data size by transferring knowledge from a malignancy classification task we developed earlier. The combined feature extraction using deep learning model and weighted extreme learning machine classifier has shown promising results for the GG prediction. This work was supported by a Research Scholar Grant, RSG-15-137-01-CCE from the American Cancer Society.

Emergency Medicine

Hariri IM, Dardas T, Kanwar M, Cogswell R, Gosev I, Molina E, Myers SL, Kirklin JK, Shah P, Pagani FD, and **Cowger JA**. Longterm Survival on LVAD Support: Limitations Driven by Development of Device Complications and End-Organ Dysfunction. *Journal of Cardiac Failure* 2020; 26(10):S143-S144.

Introduction: Survival is nearly 50% after 5 years of LVAD support. While preop variables can predict short-term (ST) survival, correlates of long term (LT) survival remain poorly characterized. Hypothesis: We hypothesize that preop risk stratification will be limited to predicting ST survival and not LT success. Method: Patients (n=16474) undergoing LVAD implant (2012-18) in Intermacs-STs were grouped according to time on support: ST (<1 year, n=4468), mid-term (MT, 1-3 years, n=8991) and LT (≥3 years, n=3015). Separate multiphase hazard analyses were performed to identify correlates of LT survival in those alive and on LVAD support at 1 and 3 years (Ys). Results: Of those alive on LVAD support at 1 Y, the 3, 5, and 6 Y survivals were 75%, 53%, and 45%, respectively. Patients who were alive on LVAD support at 3 Ys had survivals of 60% at 6 Ys. The table shows adjusted associations between clinical variables and mortality for the MT and LT survival groups starting at 1 and 3 Ys, respectively. For the MT group, older, obese and Caucasian patients and those with preop RV dysfunction, active smoking, unmarried status or comorbidities had higher mortality after 1 Y of support. The occurrence of postop malnutrition, renal, and hepatic dysfunction also increased mortality. Finally, each episode of stroke, device infection or device malfunction increased mortality by 13-42%. For the LT group, postop organ dysfunction and malnutrition impacted extended LVAD survival and mortality increased by 10-46% per adverse event. The only preop correlates of survival beyond 3 Ys were older age, Caucasian race, and history of CABG. Conclusion: The success of LVAD support hinges on achieving LT survival. In operative survivors, LT LVAD survival is heavily constrained by the occurrence of events after LVAD placement. Preop, this also limits our ability to provide individualized, LT survival estimates.

Endocrinology and Metabolism

Farlay D, Rizzo S, Ste-Marie LG, Michou L, Morin SN, **Qiu S**, Chapurlat R, **Rao SD**, and Brown J. Analysis of cortical bone quality in long-term bisphosphonate users with atypical femur fracture (AFF). *Bone Reports* 2020; 13.

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Purpose: Atypical Femur Fractures (AFF) are associated with long-term bisphosphonates (BPs) therapy, but it is unclear if cortical bone quality is altered in AFF. Accordingly, we analyze cortical bone quality in BPs-treated patients with or without AFF. Material and methods: Two groups of 26 transiliac bone biopsies from postmenopausal women treated with BPs with AFF and without AFF were analyzed. Histomorphometry revealed low remodeling in all patients. Degree of mineralization of bone (DMB) and heterogeneity index (HI) of mineralization were measured using digitized microradiography. Microhardness (Hv) was calculated with a Vickers microindenter. Quality of mineral phase and organic matrix were assessed using Fourier transform infrared microspectroscopy (FTIRM). Mann-Whitney and Spearman correlation tests were performed. Results: Women with AFF were treated significantly longer (9.7 ± 3.3 yrs) than women without AFF (7.9 ± 2.7 yrs, $p=0.026$). Cortical DMB was significantly higher in AFF than in non-AFF ($p=0.001$) and HI was significantly lower ($p=0.050$) implying a denser and more homogeneous cortical bone in AFF vs non-AFF. Increase in cortical DMB persisted even after adjustment for treatment duration ($p=0.007$). Hv and quality of mineral phase and organic matrix (FTIRM) were not modified. Cortical DMB was positively correlated with treatment duration ($r=0.468$; $p < 0.020$) in AFF group only. In contrast, denosumab, a more potent antiresorptive, lead to higher cortical DMB and lower HI as reported by us with the same methodology in 2-3 years denosumab treated women (Dempster et al. JCEM, 2018). However, Hv was significantly increased (unpublished) leading to beneficial effect on bone resistance. Conclusions: Cortical DMB was higher and HI lower in AFF than in non-AFF, but these results do not appear to be solely due to a lower bone turnover in AFF. Therefore, the combination of a higher DMB (and lower HI) and absence of higher hardness could explain the propensity for AFF in long-term BP users.

Hematology-Oncology

Dinh TK, Mitin T, Hoffman K, **Hwang C**, Karnes RJ, Kishan A, Liauw S, Lloyd S, Potters L, Showalter T, Taira A, Vapiwala N, Zaorsky N, D'Amico A, Nguyen P, and Davis B. Towards Evidence Based Practice: The American Radium Society (ARS) and American College of Radiology (ACR) Appropriate Use Guidelines on Radiation Therapy for Muscle-Invasive Bladder Cancer. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E34-E35.

Background: Definitive radiotherapy (RT), with or without concurrent chemotherapy, is an alternative to radical cystectomy for patients with localized, muscle-invasive bladder cancer (MIBC) who are either not surgical candidates or prefer organ preservation. There is a paucity of high-quality, prospective data to guide patient selection and management. Objectives: We aim to synthesize a consensus guideline regarding the appropriate use of radiotherapy based upon a systematic review of the available literature. Methods: We performed a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) literature review using the PubMed and Europe PMC databases. Articles published before and up to 3/18/2019 were included in the systematic review. Search parameters were prospectively recorded and sequentially refined for relevance of article titles. Studies were included for full manuscript review after screening of the abstracts. Based upon findings of the literature review, critical management topics were identified and reformulated into consensus questions. An expert panel was assembled to address key areas of both consensus and controversy. Results: A total of 761 articles were screened, of which 60 were published between 1975 to 2019 and included for full review. Of these, there were seven well-designed studies, 20 good quality studies, 27 quality studies with design limitations, and six references not suited as primary evidence. While early studies included node-positive MIBC, contemporary trials mostly exclude this population from definitive radiotherapy treatments. Adjuvant radiotherapy after cystectomy was not included due to lack of high-quality data or clinical utilization. An expert panel consisting of 14 radiation oncologists, one medical oncologist, and one urologist from 14 institutions was assembled. We identified four clinical variants of MIBC: surgically fit patients who wish to pursue organ preservation; patients surgically unfit for cystectomy; patients medically unfit for cisplatin-based chemotherapy; and borderline cystectomy candidates based on age with unilateral hydronephrosis and normal renal function. After synthesis of the evidence, we identified key areas of controversy, including use of definitive radiotherapy for patients with negative prognostic factors (e.g. hydronephrosis, multifocal disease, extensive CIS), appropriate radiotherapy dose, fractionation, fields and technique when used, and chemotherapy sequencing and choice of agent. Conclusions: A systematic review of the literature was performed to assess the evidence for radiotherapy for patients with localized MIBC. Overall, there is a paucity of level-one evidence to guide clinical practice. Studies vary significantly with regards to

patient selection, chemotherapy utilization, and radiotherapy technique. A consensus guideline on the appropriateness of RT for MIBC may aid practicing oncologists in bridging the gap between data and clinical practice.

Hematology-Oncology

Schrezenmeier H, Hill A, Piatek CI, de la Tour RP, Lee LWL, Wells R, Brodsky R, Kim JS, Nishimura J, **Kuriakose P**, Pavani R, Liu P, Ortiz S, Lee JW, and Kulasekararaj A. Breakthrough hemolysis in adult patients with paroxysmal nocturnal hemoglobinuria treated with Ravulizumab: Results of a 52-week extension from two phase 3 studies. *Oncology Research and Treatment* 2020; 43(SUPPL 4):177-178.

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Internal Medicine

Al-Abcha A, **Elkhatib L**, Boumegouas M, Kemnic T, and Herzallah K. TCT CONNECT-245 A Meta-Analysis of Drug-Coated Balloon Versus Drug-Eluting Stent in De Novo Small Vessel Coronary Artery Disease. *Journal of the American College of Cardiology* 2020; 76(17):B108-B109.

Background: Revascularization of small vessel coronary artery disease (SvCAD) is associated with high rate of adverse clinical outcomes. Drug-coated balloon (DCB) is an emerging alternative to drug-eluting stent (DES) in de novo SvCAD. There is limited data about the safety and outcomes of DCB in de-novo SvCAD. Methods: A meta-analysis was conducted of all studies that compared DCB and DES in de novo SvCAD. This analysis included studies with at least a 1-year follow-up from inception until April 2020. The primary outcome was all-cause mortality. Secondary outcomes included myocardial infarction, and target lesion revascularization. Following an extensive search, this is the first study to include the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) report. Results: Six studies with a total of 16,591 patients were included. The median-weighted follow-up period was 2.8 years. Two of the 6 studies (BELLO [Balloon Elution and Late Loss Optimization] and BASKET-SMALL2 [Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions]) were randomized clinical trials, whereas the rest were observational studies. Heterogeneity was low to moderate across the trials (14% to 54%). In terms of the primary outcome, there was no significant difference in all-cause mortality between DCB and DES (Figure). There was also no significant difference found in the secondary outcomes of myocardial infarction and target lesion revascularization between the 2 groups (Figure). [Formula presented] Conclusion: This meta-analysis suggests similar clinical outcomes of DCB-treated versus DES-treated de novo SvCAD. According to these results, DCB can be considered as a reasonable treatment option for SvCAD. However, further data including large randomized clinical trials are needed to confirm these results. Categories: CORONARY: Drug-Eluting Balloons and Local Drug Delivery

Internal Medicine

Ijaz N, Taleb I, Kyriakopoulos CP, **Demetris Z**, **Peruri A**, Richins TJ, Dranow L, Tang D, **Nemeh H**, Stehlik J, Koliopoulou AG, Selzman CH, Alharethi R, **Cowger J**, Shah P, and Drakos SG. A Novel Risk Score Predicts Early Right Ventricular Failure after Lvad: A Derivation-validation Multicenter Study. *Journal of Cardiac Failure* 2020; 26(10):S149.

Introduction: Right ventricular failure (RVF) after LVAD implantation is associated with increased morbidity and mortality. Despite several RVF predictive models, poor performance in external validation cohorts has limited their widespread clinical adoption. Objective: To develop a novel RVF predictive model, ascertain its performance in an independent validation cohort, and develop an RVF risk score. Methods: Consecutive LVAD patients were prospectively enrolled at the Utah Transplantation Affiliated Hospitals (U.T.A.H) Cardiac Transplant Program (n=477, Derivation cohort). LVAD patients from Inova Heart & Vascular Institute and Henry Ford Medical Center formed the external dataset (n=321, Validation cohort). The primary outcome was early RVF, defined as the need for RVAD or intravenous inotropes for >14 days. The secondary outcome was 3-year all-cause mortality. Multivariable logistic regression analysis was used to develop a predictive model. An RVF risk score was developed using weighted points based on the β -regression coefficients of the multivariable predictors. Results: The study included 798 patients, with a mean age of 56y, 84% male, and 30% INTERMACS Profile 1-2. Compared to the derivation cohort, the validation cohort had a higher proportion of African-Americans (37% vs 7%; $p<0.01$), patients with a history of HTN (60% vs 49%; $p=0.002$), and bridging to durable LVAD with short-term MCS (16% vs 8%; $p<0.01$). The incidence of RVF in the derivation and validation cohorts was 16% and 36%, respectively. Multivariable analysis yielded 7 factors associated with RVF (African-American, history of HTN, INTERMACS profile 1-2, Na $<130\text{mEq/L}$, BUN $>35\text{mg/dL}$, PA pulse pressure $<36\text{ mmHg}$ and RA/PCWP >0.5). The model had a c-statistic of 0.73 ([95% CI:0.67-0.79]; $p<0.01$) and 0.71 ([95% CI: 0.65 - 0.77]; $p<0.01$) in the derivation and validation cohorts, respectively. A 10-point RVF risk score was developed (Table). The presence of RVF was associated with a higher 1-year (33% vs 12%; $p<0.01$) and 3-year (39% vs 19%; $p<0.01$) mortality. Conclusion: We propose a novel scoring system to predict post-LVAD RVF, achieving high discriminative performance after being tested in distinct and highly heterogeneous populations. This simple predictive tool could impact patient selection and perioperative management of LVAD patients.

Internal Medicine

Isseh IN, **Gorgis S**, **Dagher C**, **Sharma S**, **Basir MB**, and **Parikh S**. Escalating Temporary Mechanical Circulatory Support In Worsening Cardiogenic Shock: Feasibility In Advanced Heart Failure Therapy Candidates. *Journal of Cardiac Failure* 2020; 26(10):S55.

Background: Temporary mechanical circulatory support (tMCS) can be used in cardiogenic shock (CS) as a bridge to advanced heart failure therapies (AHFT) (durable LVAD, cardiac transplantation). tMCS escalation in worsening CS has never been studied and prognostication in this cohort is needed, particularly in candidates for AHFT. We evaluated potential predictors of survival and outcomes of those that received AHFT. Methods: From 07/2016-07/2018 we identified patients with worsening CS shock requiring tMCS escalation. Worsening CS was defined as persistent hypotension; increasing doses of vasopressors/inotropes; worsening end-organ perfusion parameters; and/or worsening invasive hemodynamics. tMCS escalation was defined as adding/exchanging tMCS device to existing tMCS. Potential prognostic variables were evaluated in ROC curves. All statistical tests were performed with a two-sided $p\text{ value}=0.05$. Results: 81 consecutive patients ($61\pm 14\text{y}$, 73% m) had worsening CS shock requiring tMCS escalation. Devices used were IABP, Impella (2 5, CP, 5 0), ECMO and Tandem (TandemHeart, TandemLife, ProtekDuo). Survival to discharge was 32%. Etiology of shock was heterogeneous (33% AMI; 62% decompensated heart failure). 62% were transfers from outside hospitals. Utilization of a PA catheter pre-escalation was associated with improved survival compared to absence of a PA catheter (40% vs 18%, $p=0.05$). ROC curves demonstrated prognostic thresholds associated with survival: age $<53\text{y}$ (80% specificity) and pre-escalation cardiac power output (CPO) $>0.92\text{ Watts}$ (87% specificity). While prognostic thresholds associated with mortality were: age $>69\text{ y}$ (81% specificity), BMI $>35\text{ kg/m}^2$ (81% specificity), pre-escalation cardiac power output (CPO) $<0.53\text{ Watts}$ (82% specificity), pre-escalation lactate $>3\text{ mmol/L}$ (81% specificity). AUC was greatest in post-escalation blood pressure indicating persistence of hypotension post-escalation (SBP $<85\text{ mmHg}$; MAP $<67\text{ mmHg}$) was associated

with a dismal prognosis (specificity 92% for both for predicting mortality). 7 patients went on to receive AHFT (49±13.4y, 57%_m) with a mean BMI 32±11.4 kg/m². 6 received durable LVAD during index hospitalization, 4 of which survived. 4 underwent transplant in subsequent hospitalizations, all of which survived. Majority had decompensated heart failure as etiology of shock (NICM=5, ICM=1, AMI=1) and received tMCS escalation within 1 day (n=6). All patients were classified as Stage D SCAI CS at the time of escalation and 5 received vasopressors/inotropes. Majority of patients had a PA catheter at time of escalation (n=6). Overall survival was higher in the AHFT compared to those that did not receive AHFT (n=5, 71% vs n=21, 28.4%, p=0.03). Conclusions: tMCS escalation in worsening CS incurs poor survival overall (32%). tMCS escalation is feasible in stabilizing patients with worsening CS that are candidates for AHFT.

Internal Medicine

Michaels AT, Peterson E, Luzum J, Gui H, Pinto Y, Sabbah HN, Williams LK, Snider J, and Lanfear DE. Biomarker Guided Therapy For Heart Failure With Mid-Range EF. *Journal of Cardiac Failure* 2020; 26(10):S37.

Background: Heart failure (HF) with mid-range ejection fraction (HFmrEF, EF 40-49%) accounts for ~15% of HF patients and these are a heterogeneous group with a phenotypic character that reflects aspects of both preserved and reduced EF HF. There are no proven treatments for this group but identifying subsets of patients that will respond to conventional therapies such as beta blockers (BB) would be desirable. We hypothesized that HFmrEF patients with elevated Nt-proBNP or ST2 would have more favorable response to BB therapy. Methods: A prospective registry was conducted that enrolled 1760 HF patients who met Framingham HF criterion and who received care through our health system and insurance product. Participants donated blood for biomarker measurements at enrollment and their medication exposure was quantified over time using pharmacy claims data. The current study utilized all participants who had EF 40-49% and baseline biomarker measurement (n=338). The primary endpoint was all-cause mortality. Biomarker categories were dichotomized at Nt-BNP >1000ng/L and ST2 ≥35ng/mL. We quantified the HR for BB exposure overall and divided by biomarker level using Cox models adjusted for MAGGIC score and BB propensity score. Results: Vital status and Nt-BNP measurements were available for all 338 patients, while 279 had ST2 measured, and 201 had both markers (Table 1). For Nt-BNP, 200 (58%) had elevated levels while 143 (42%) had low values. BB use in patients with elevated Nt-BNP levels had a hazard ratio (HR) of 0.43 (p=0.1) compared to HR 0.97 (p=0.97) in the low Nt-BNP group. For ST2, 195 patients (70%) had levels <35 ng/mL while 84 (30%) had elevated levels. BB use in the elevated ST2 cohort had a HR 0.08 (p=0.71) vs. 0.62 (p=0.72) in the low ST2 group, a statistically significant interaction. (p_{int}= 0.089). Both low marker groups had very low event rates (3.5% and 3.1% 1 year death, respectively). The combination of the two markers together (either elevated vs. both low) identified an especially low risk group with 1.5% dying and predicted the BB benefit association; in the low marker group BB HR =0.99 (p >0.99) while in patients with either ST2 or Nt-BNP elevated the BB HR was 0.06 (p=0.03). Conclusions: In this observational study of HFmrEF patients, those with low ST2 and Nt-BNP have low risk of death and little benefit of BB therapy whereas among the approximately two-thirds of patients with either marker elevated a substantial BB benefit association was seen

Obstetrics, Gynecology, and Women's Health

Rattan R, Dimitrova I, Udumula MP, Buekers TE, and Giri S. Calorie restriction for ovarian cancer reduction. *Gynecologic Oncology* 2020; 159:118-119.

Objective: Dietary interventions are attractive as inexpensive supportive anticancer therapies. Calorie restriction is an established tumor preventive regimen, reducing systemic inflammation and growth factor signaling, as well as improving metabolic markers in the tumor. The aim of our study was to determine the effect of calorie restriction on ovarian cancer outcome. Method: Female B6 mice were fed either ad libitum or underwent a 30% calorie restriction. After 5 weeks, mouse epithelial ovarian cancer (EOC) ID8 cells (5 million cells) were injected intraperitoneally. Tumor growth was monitored by in situ luciferases guided imaging, followed by pathological determination of tumors at 8 weeks. Changes in growth factors/cytokines were determined by ELISA, and immune response was measured by flow cytometry analysis. Results: The mice on calorie restriction displayed decreased EOC burden in contrast to mice fed ad libitum (P < 0.01). The mice on calorie restriction exhibited increased survival (median survival 100

days) in contrast to mice fed ad libitum (median survival 70 days, $P < 0.01$). The calorie-restricted mice showed a significant reduction in levels of insulin, leptin, MCP-1, VEGF, and IL-6 (P ranging from 0.5 to 0.01). In addition, calorie-restricted mice had increased frequency of T cells (CD4, CD8, and NKT cells) and decreased frequency of macrophages ($P < 0.05$). Conclusion: Our study suggests that calorie restriction can suppress ovarian cancer growth and is associated with modulation of inflammatory and immune microenvironment, suggesting the promise of calorie restriction and its mimetics as supportive anticancer therapies.

Obstetrics, Gynecology, and Women's Health

Udumula MP, Dimitrova I, Sakr S, Buekers TE, Giri S, and Rattan R. Omega-3 lipid metabolites as mediators of metformin's anti-proliferative effect in ovarian cancer. *Gynecologic Oncology* 2020; 159:124.

Objective: Metformin is being repurposed for treatment of gynecologic malignancies and other cancers. It is known to alter the cancer cell metabolism, primarily the energy metabolism. Our aim was to identify and test the preclinical efficacy of the prominent metabolite changes occurring in response to metformin treatment in ovarian cancer cell lines. Method: Three human ovarian cancer cell lines (A2780, C200, and SKOV3IP) treated with metformin (10 mM) for 48 hours were subjected to untargeted global metabolomics by ultra-high-performance liquid chromatography and gas chromatography mass spectrometry. Statistical and bioinformatics analyses were performed. Five ovarian cancer cell lines (A2780, C200, SKOV3IP, ID8, and OVCAR5) with different genetic makeups and characteristics were treated with varying doses of omega-3 metabolites (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) (12.5–200 μ M) with or without carboplatin. Cell survival was assayed by MTT and clonogenic assay (12.5–100 μ M). SKOV3 and CaoV3 xenograft models were used for testing the preclinical efficacy of DHA and EPA. Results: Under metformin treatment, the 3 cell lines revealed 57 common altered metabolites, of which 30 had consistent direction change. The enrichment analysis of the commonly upregulated metabolites indicated a universal increase of the omega-3 biosynthetic pathway, including alpha-linolenic and linoleic acid metabolism ($P < 0.001$). Treatments with EPA or DHA, the most common lipids from the pathway, resulted in a significant dose-dependent inhibition of proliferation in all 5 cell lines ($P < 0.001$). EPA and DHA potentiated carboplatin cytotoxicity in all cell lines ($P < 0.05$). Significant inhibition of colony formation was also noted with EPA and DHA ($P < 0.01$). Treatment with EPA and DHA significantly improved the survival of mice bearing SKOV3 and CaOv3 xenograft tumors ($P < 0.01$). Conclusion: Metformin treatment resulted in increase of omega-3 fatty acid metabolism. Both EPA and DHA, metabolites of the pathway, inhibited ovarian cancer cell proliferation alone and in combination with carboplatin, as well as increased survival in ovarian cancer mouse models. Thus, the cytotoxic effect of metformin may be partially mediated through upregulation of omega-3 lipids.

Neurology

LeWitt PA, Stocchi F, Ferreira JJ, Klepitskaya O, Magalhaes D, Rocha JF, and Soares-da-Silva P. Efficacy of Opicapone at Different Levodopa Regimens up to a Threshold of 600mg/Day Levodopa in Parkinson's Disease Patients with Motor Fluctuations. *Annals of Neurology* 2020; 88:S187-S188.

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Neurology

Rattan R, Dimitrova I, Udumula MP, Buekers TE, and Giri S. Calorie restriction for ovarian cancer reduction. *Gynecologic Oncology* 2020; 159:118-119.

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Objective: Dietary interventions are attractive as inexpensive supportive anticancer therapies. Calorie restriction is an established tumor preventive regimen, reducing systemic inflammation and growth factor

signaling, as well as improving metabolic markers in the tumor. The aim of our study was to determine the effect of calorie restriction on ovarian cancer outcome. Method: Female B6 mice were fed either ad libitum or underwent a 30% calorie restriction. After 5 weeks, mouse epithelial ovarian cancer (EOC) ID8 cells (5 million cells) were injected intraperitoneally. Tumor growth was monitored by in situ luciferases guided imaging, followed by pathological determination of tumors at 8 weeks. Changes in growth factors/cytokines were determined by ELISA, and immune response was measured by flow cytometry analysis. Results: The mice on calorie restriction displayed decreased EOC burden in contrast to mice fed ad libitum ($P < 0.01$). The mice on calorie restriction exhibited increased survival (median survival 100 days) in contrast to mice fed ad libitum (median survival 70 days, $P < 0.01$). The calorie-restricted mice showed a significant reduction in levels of insulin, leptin, MCP-1, VEGF, and IL-6 (P ranging from 0.5 to 0.01). In addition, calorie-restricted mice had increased frequency of T cells (CD4, CD8, and NKT cells) and decreased frequency of macrophages ($P < 0.05$). Conclusion: Our study suggests that calorie restriction can suppress ovarian cancer growth and is associated with modulation of inflammatory and immune microenvironment, suggesting the promise of calorie restriction and its mimetics as supportive anticancer therapies.

Neurology

Udumula MP, Dimitrova I, Sakr S, Buekers TE, Giri S, and Rattan R. Omega-3 lipid metabolites as mediators of metformin's anti-proliferative effect in ovarian cancer. *Gynecologic Oncology* 2020; 159:124.

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Objective: Metformin is being repurposed for treatment of gynecologic malignancies and other cancers. It is known to alter the cancer cell metabolism, primarily the energy metabolism. Our aim was to identify and test the preclinical efficacy of the prominent metabolite changes occurring in response to metformin treatment in ovarian cancer cell lines. Method: Three human ovarian cancer cell lines (A2780, C200, and SKOV3IP) treated with metformin (10 mM) for 48 hours were subjected to untargeted global metabolomics by ultra-high-performance liquid chromatography and gas chromatography mass spectroscopy. Statistical and bioinformatics analyses were performed. Five ovarian cancer cell lines (A2780, C200, SKOV3IP, ID8, and OVCAR5) with different genetic makeups and characteristics were treated with varying doses of omega-3 metabolites (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) (12.5–200 μ M) with or without carboplatin. Cell survival was assayed by MTT and clonogenic assay (12.5–100 μ M). SKOV3 and CaoV3 xenograft models were used for testing the preclinical efficacy of DHA and EPA. Results: Under metformin treatment, the 3 cell lines revealed 57 common altered metabolites, of which 30 had consistent direction change. The enrichment analysis of the commonly upregulated metabolites indicated a universal increase of the omega-3 biosynthetic pathway, including alpha-linolenic and linoleic acid metabolism ($P < 0.001$). Treatments with EPA or DHA, the most common lipids from the pathway, resulted in a significant dose-dependent inhibition of proliferation in all 5 cell lines ($P < 0.001$). EPA and DHA potentiated carboplatin cytotoxicity in all cell lines ($P < 0.05$). Significant inhibition of colony formation was also noted with EPA and DHA ($P < 0.01$). Treatment with EPA and DHA significantly improved the survival of mice bearing SKOV3 and CaOv3 xenograft tumors ($P < 0.01$). Conclusion: Metformin treatment resulted in increase of omega-3 fatty acid metabolism. Both EPA and DHA, metabolites of the pathway, inhibited ovarian cancer cell proliferation alone and in combination with carboplatin, as well as increased survival in ovarian cancer mouse models. Thus, the cytotoxic effect of metformin may be partially mediated through upregulation of omega-3 lipids.

Neurosurgery

Wen N, Dai Z, Carver E, Liang E, Snyder J, Griffith B, and Movsas B. Glioblastoma MR Images Synthesis with Generative Adversarial Network. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E28.

Background: Automatic delineation of Glioblastoma (GBM) plays an important role in radiation therapy. Recently, segmentation algorithms using supervised deep neural networks (DNN) have shown promising results, but small volumes of annotated data pose challenges on powering them. Current collection of dataset relies on radiologists' contour as ground truth and is expensive and time-consuming. Objectives: One possible solution to overcome the limitation of small dataset is to generate synthetic MR images

representing different clinical scenario. The aim of this study is to apply a generative adversarial network (GAN) to synthesize highly realistic MR images from manipulated annotations that are able to feed as new training samples for DNNs. Methods: Data was obtained from the BraTS multimodal Brain Tumor Segmentation Challenge 2018. 19 different institutions provided a total of 210 patients. T1WI, T1CE, T2WI, and FLAIR were provided for each patient. 82 patients were used for training and 128 patients for validation. The network consisted of a generator and two discriminators. Image per-pixel loss, perceptual loss and adversarial loss were used. By manipulating on annotations from radiologists, the generator was able to output new synthetic MR images, and boost the size of dataset. The realism of synthetic images was evaluated both quantitatively and qualitatively. Results: Synthetic image generated from non-manipulated annotation was compared with its corresponding real image. Mean Square Error (MSE), Mean Absolute Error (MAE), Peak Signal to Noise Ratio (PSNR), and Structural Similarity Index (SSIM) for synthetic MR images were 19.246 ± 0.308 , 23.375 ± 0.586 , 43.068 ± 0.443 and 0.788 ± 0.002 ; 19.249 ± 0.274 , 22.805 ± 0.583 , 43.054 ± 0.437 and 0.789 ± 0.004 ; 19.246 ± 0.290 , 23.391 ± 0.400 , 43.102 ± 0.45 and 0.784 ± 0.003 ; 18.930 ± 0.40 , 24.119 ± 1.48 , 43.126 ± 0.46 and 0.794 ± 0.005 , respectively, for T1, T1CE, T2 and Flair. A subset of 9 real and 10 generated patients were assessed by a physician. 8.3%, 41.7%, 50% of real images and 22.5%, 47.5%, 30% of synthetic images were commented as poor, marginal and good quality. The misclassified rate were 26.3%, 10.5%, 26.3% and 26.3% for T1, T1CE, T2 and Flair. Conclusions: We proposed to apply GAN to synthesize GBM MR images from manipulated annotations to increase the dataset size to train deep learning segmentation models. The evaluation results showed synthetic MRIs had comparable image quality to real MRIs that had potential to be used for DNN training.

Otolaryngology

Ghanem A, Schymick M, Khalil R, Williams A, and Siddiqui F. Does the use of Marijuana Impact Outcomes in Patients with Squamous Cell Carcinoma of the Oropharynx? *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E42.

Background: The incidence of human papilloma virus (HPV) associated oropharyngeal squamous cell carcinoma (OP-SCC) has increased significantly in the past few years. While many of these patients do not abuse tobacco products, they may use marijuana in various forms. The impact of marijuana use/abuse on survival and local control in head and neck cancer patients is not well understood. Objectives: The purpose of our analysis was to evaluate the management and outcomes in our patients treated for OP-SCC stratified according to marijuana use. Methods: After obtaining Institutional Review Board (IRB) we used our institutional database of 360 patients with detailed psychosocial and substance abuse history to identify patients with OP-SCC. Clinico-pathological data and treatment details were compared between marijuana users vs. non-users. Using Kaplan-Meier curves and log-rank test were evaluated overall (OS), disease free (DFS), distant metastases free (DMFS) and locoregional free (LRFS) survival based on Marijuana use. Results: We identified 74 patients with OP-SCC of which 62 (84%) were male, 55 (74%) were Caucasians and 52 (70%) were HPV+ve. Median age was 62 years (range: 41-71) and 61% were ever-smokers with median pack/year of 25.5. Radical surgery was undergone in 17 (23%), whereas, the rest 57 (77%) were treated by definitive chemoradiotherapy. Marijuana users encompassed 35% of the study cohort (n=26) and non-users were 65% (n=48). Clinicopathological details not differ between the study groups. In addition, marital status, highest educational level, alcohol use and smoking history were similar. Marijuana users underwent marginally less surgeries (11.5 vs 29.2%; p=0.085), had higher median pain score (7 vs. 6) and more mean weight loss during radiotherapy (22.2 vs 18.5 Lb.), albeit nothing was significant (p>0.05). Although LRFS (p=0.12) and DMFS (p=0.48) did not differ between users vs. non-users; marijuana use was marginally detrimental for DFS (1-year 69% vs. 77% and 3-years: 27% vs. 70%; p=0.051) and was associated with significantly worse OS (1-year: 60% vs. 82% and 3-years: 30% vs. 73%; p=0.005). Conclusions: Marijuana use was not associated with disease specific features. Nevertheless, there seems to be a significant impact of the use of marijuana and the adherence to RT, quality of life, and overall survival. A more detailed analysis is underway to better understand the impact of various psycho-social factors on RT treatment tolerance.

Otolaryngology

Margalit D, Sacco A, Bakst R, Beadle B, Beitler J, **Chang S**, Chen A, Cooper J, Galloway T, Koyfman S, Ridge J, Robbins J, Truong MT, Tsai CJ, Yom S, and **Siddiqui F**. Postoperative Therapy for Resected Squamous Cell Carcinoma of the Head and Neck (SCCHN): Initial Findings of an American Radium Society (TM) (ARS) Appropriate Use Criteria Systematic Review (SR). *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E44.

Background: Progress in SCCHN management requires re-evaluation of postoperative therapy for resected SCCHN. Since the ARS and American College of Radiology (ACR) published a literature review and expert consensus guideline on postoperative therapy in 2011, additional relevant clinical trials have been published. Objectives: To comprehensively evaluate existing prospective clinical studies of postoperative therapy for resected SCCHN using a formalized methodologic approach described by the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Protocol, and to identify areas of accepted recommendations, controversy and uncertainty. Methods: The methodologic protocol for this SR was guided by PRISMA. Ovid Medline and Embase were searched on 01/10/2019 using medical subject headings designed to capture all published studies of HN cancer and postoperative therapy. The PICO (participants, interventions, comparators, outcomes) framework was used to identify published randomized trials, single and multi-arm non-randomized prospective clinical trials, and SRs/meta-analyses that adhered to a published methodology. Longitudinal prospective cohort studies were included if there was a baseline pre-intervention assessment. Excluded studies had <20 patients, were in non-English languages, or were case reports, case series, retrospective studies, large database studies, abstracts, preliminary analyses, narrative reviews, modeling studies, cell-line or non-clinical/non-human studies. Articles were selected if the population included adult patients with stage I-IVB SCCHN and no prior HN radiation who were treated with curative-intent surgery. Included disease sites were: oral cavity, oropharynx, hypopharynx, and larynx. The interventions of interest were postoperative radiation therapy (PORT), chemo-PORT, or postoperative chemotherapy, biologic therapy, targeted therapy, and/or immunotherapy. Studies were selected using Covidence® software by two independent reviewers based on study relevance related to the inclusion/exclusion criteria. Each study was graded using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence Table. Results: A total of 5,689 studies were identified. After removal of duplicates, 5,660 studies were screened using the title and abstract, leading to 201 studies assessed for relevance using full-text review. After limitation to the eligibility criteria, 96 studies were identified. An additional 4 eligible studies were added that were published after the cut-off date or were not identified through the literature search. Studies with primary oncologic endpoints included 11 SRs, 24 randomized trials, 28 non-randomized trials, and 9 post-hoc analyses of randomized trials. Studies of non-oncologic endpoints included 2 SRs, 1 randomized trial, and 21 non-randomized clinical trials. Conclusions: This comprehensive, rigorously conducted SR identified 96 published prospective studies of postoperative therapy for SCCHN that constitute the evidence base for the ARS AUC HN Committee's systematic review. Recommendations and identification of areas of continuing disagreement requiring further research will be generated from this evidence base; these will be described in more detail at the time of presentation.

Otolaryngology

Tsai CJ, Galloway T, Beitler J, Cooper J, Bakst R, Ridge J, Beadle B, Robbins J, Chen A, Sacco A, **Chang S**, Truong M, Koyfman S, Yom S, and **Siddiqui F**. Ipsilateral Radiation for Squamous Cell Carcinoma of the Tonsil: Summary of Findings and Controversies from the ARS Appropriate Use Criteria Expert Panel on Tonsil Cancer. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E41-E42.

Background: In 2012 the American College of Radiology (ACR) published the Appropriateness Criteria for Ipsilateral Radiation for squamous cell carcinoma (SCC) of the tonsil. Since then there have been additional advancements and publications pertinent to this topic. Objectives: We performed an updated literature review and summarize the findings as well as potential controversies. Methods: We performed a PubMed search of articles published between January 2000 and June 2019 using various combinations of 25 pre-determined keywords and restricted to articles having the full text available, written in the English language, and on human subjects. Of the 46 citations returned from the search, the authors added 3 citations from bibliographies, websites or books not found in this literature search. Of the 49

citations, 30 citations were retained for further detailed review, and 14 of them were added to the evidence table. Articles were removed from the bibliography if they were not relevant or generalizable to the topic, focused on unknown primary disease, or they were no longer cited in the revised narrative text. Each study was graded using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence Table. Results: For clinically staged patients undergoing primary (chemo)radiotherapy, we identified 11 new articles published since the initial ACR guideline. Similar to the recommendation in the earlier guideline, unilateral radiotherapy was most often recommended for patients with tumors that were tonsil-confined or either > 1 cm from midline or involving \leq 1 cm of the mucosa of the base of tongue and/or soft palate. The published experiences demonstrated low rates of contralateral failure in both p16+ and p16- subsets. For patients undergoing primary tumor surgery and being considered for adjuvant radiotherapy, 3 new articles were identified. Multi-disciplinary evaluation is highly recommended before surgery or radiation, since surgical considerations for tonsil cancer may differ from those relevant to ipsilateral RT. The definitions of “well-lateralized” tonsil cancer from a surgical perspective could differ from that of a radiation oncologist. Consequently, whether all surgically resected T1-T2 tonsil SCC with a clinically node-negative contralateral neck are candidates for ipsilateral adjuvant RT warrants further discussion. Collectively among all of the literature reviewed, 1,031 patients were selected for either primary or adjuvant ipsilateral radiotherapy; 26 of 1,031 cases experienced contralateral disease progression. Of these, 19 were reported to have successful salvage and disease control at time of publication. Less than 1% (7 of 1,031) of patients managed unilaterally experienced contralateral progression that was not successfully salvaged. Other factors that might impact the selection for unilateral therapy but remain controversial include: patient age, performance status, number and size of ipsilateral nodes, number of involved ipsilateral nodal stations, clinical/pathological extranodal extension, and p16 status. Conclusions: This updated literature search provided additional information relevant to selection of patients for ipsilateral tonsil radiotherapy in the primary and adjuvant setting. Areas of controversies identified will require further reconciliation and investigation. Updated voting and committee recommendations will be presented.

Pharmacy

Attar D, Lekura J, Kalus JS, Al-Darzi W, Williams CT, and Grafton GF. Impact of A Pharmacist-Led Heart Failure Clinic on Guideline-Directed Medical Therapy. *Journal of Cardiac Failure* 2020; 26(10):S129.

Introduction: ACE-I/ARBs, beta-blockers (BB), and aldosterone antagonists are standard of care for patients with heart failure and reduced ejection fraction (HFrEF). Studies have shown that a pharmacist-managed heart failure (HF) medication titration clinic increases the percentage of patients on optimal doses of ACE-I/ARB and BB. Pharmacists' role in improving follow-up, increasing access to HF medications, and impacting clinical outcomes is not well described in the literature. Hypothesis: Including pharmacists in a HF clinic for management of HFrEF leads to greater achievement of target doses of guideline-directed medical therapy (GDMT) within 3 months of an initial visit. Methods: This was a prospective, quasi-experimental study comparing patients with HFrEF seen in a pharmacist-run HF clinic to patients managed by usual care. Patients whose initial visit was between September 2019 and January 2020 were included. The primary endpoint was number of patients who reached target or maximally tolerated doses of GDMT within 3-months of the initial visit. Initial and follow up encounters occurred via face-to-face visits in both groups. Secondary endpoints included number of encounters, medication changes, time to follow-up post-discharge, and number of patients considered for ARNI. Results: Thirty-nine patients in the pharmacist group and 35 patients receiving usual care were included. Fifteen of the 39 patients were referred to a pharmacist during hospital admission. Within the pharmacist group, the median time to follow up post-discharge was 15 days (IQR, 10.5 - 21.5) with a pharmacist and 31 days (IQR, 24 - 41) with a cardiologist. Including those lost to follow up, GDMT at target doses was achieved in 23/39 in the pharmacist group versus 4/35 in the usual care group (59% vs 11.4 %; P < 0.001) (Table 1). Patients in the pharmacist group were seen more frequently and were more likely to receive HF education, ARNI consideration, and medication changes over 3-months (Table 2). Conclusions: Pharmacist involvement in HFrEF management improves patient care with achievement of GDMT earlier than usual care and more frequent follow-up. Other benefits include HF education, greater consideration for ARNI, and earlier access to a healthcare provider after hospital discharge.

Public Health Sciences

Cook A, Khalil R, Burmeister C, and Elshaikh M. The Impact of Different Adjuvant Managements on Survival Endpoints in Women with Adequate Surgical Staging Early Stage Uterine Serous Carcinoma. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E36.

Background: Non-endometrioid carcinomas, which includes uterine serous carcinoma (USC), comprise only 15% of all endometrial carcinomas but cause about 40% of deaths in this patient population. The ideal adjuvant management of patients with early-stage USC is remains unknown. Objectives: To report survival outcomes in women with early stage USC after adequate surgical staging with various adjuvant management options. Methods: After IRB study approval, our prospectively-maintained database for women with endometrial carcinoma was queried for women with 2009 International Federation of Gynecology and Obstetrics (FIGO) stages I-II USC based on WHO pathologic definition who underwent adequate surgical staging between 1/1991 and 4/2017 followed by adjuvant management [surveillance, radiation treatment (RT) or chemotherapy (CT) or combination (CRT)]. Chi-squared tests were performed to compare differences in outcome by type of adjuvant management. Recurrence-free (RFS), disease-specific (DSS) and overall survival (OS) were assessed by Kaplan-Meier and log-rank tests. Univariate and multivariate analyses were performed to identify statistically significant predictors of survival endpoints. Results: We identified 155 women who met our inclusion criteria. The median follow-up time was 54.8 months. 75% of the study cohort were with stage IA, 14% stage IB and 11% with stage II. All women underwent pelvic lymph node dissection with a median number of dissected lymph nodes of 15. Omentectomy was performed in 62% of women. Adjuvant RT was utilized in 55% of women (54 with vaginal brachytherapy alone, 22 with pelvic RT and 10 with combination). Most commonly used chemotherapy was carboplatin and paclitaxel with a median number of cycles of 6 5-year RFS was 78% for those received CRT, 84% for RT alone, 65% who received CT alone and 48% for those who were observed ($p=0.03$). 5-year DSS was 79%, 92%, 66% and 53%, respectively ($p=0.02$). 5-year OS was 76%, 79%, 63% and 53%, respectively ($p=0.21$). On multivariate analysis of OS, old age, and not receiving any adjuvant therapies were independent predictors of worse OS. Independent predictors of better RFS and DSS included adjuvant RT alone or with chemotherapy, and lack of lymphovascular space invasion. Conclusions: In this cohort of women with adequate surgical staging, adjuvant radiation treatment with or without chemotherapy is associated with reduced tumor recurrence with improved survival endpoints.

Public Health Sciences

Janic B, Brown S, Neff R, Liu F, Bobbitt K, Mao G, Chetty I, Movsas B, and Wen N. Radiation and Gold Nanoparticle Increase the Expression of Immunogenic Cell Death Markers in MDA MB 231 Breast Cancer Model. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E26-E27.

Background: Tumor immunogenic cell death (ICD) plays a major role in stimulating host anti-cancer immune response that can determine the success of cancer radiotherapy (RT). Additionally, ICD can also be induced by radiation itself. The main feature of ICD is the release of immunogenic molecules by dying cells, termed damage associated molecular patterns (DAMPs) that act on innate and adaptive immune components to induce long-lasting antitumor immunity. Two breast cancer (BCa) DAMPs involved in phagocytosis and dendritic cell antigen presentation are Calreticulin (CLR) and HMGB1; loss of HMGB1 expression is linked to poor clinical prognosis. Therefore, these molecules are being studied for their therapeutic and prognostic potential. As RT, either alone or in combination, is often part of standard BCa therapies, the effect of RT and radiosensitizers, such as gold nanoparticles (AuNPs), on DAMPs expression must be considered when designing new protocols, especially if combining RT with an adjuvant mode such as immunotherapy. Objectives: The goal of this study was to measure the effect of radiation on CLR and HMGB-1 expression in the presence and absence of a novel AuNP radiosensitizer in MDA MB 231 BCa in vitro and in vivo models. We hypothesized that AuNP modulates radiation induced ICD by altering CLR and HMGB1 expression. Methods: In vitro: MDA MB 231 cells were incubated for 3h with 14nm AuNPs and irradiated. After 48h and 72h the percentages of CLR and HMGB1 positive cells were determined by flow cytometry. In vivo: Female nude mice bearing MDA MB 231 tumors received intratumoral injections of 14 nm AuNPs. After 24h mice were irradiated with 15 Gy dose using 160 kV photons. Mice were euthanized, histological sections prepared, stained with anti CLR antibodies and analyzed by light microscopy. Results: In vitro, radiation induced increase in the

percentages of CLR and HMGB1 positive cells was potentiated by AuNP at 48h and 72h time points. In control cells, AuNP alone increased the percent of HMGB1 positive cells at both time points. The percent of CLR positive cells was increased at 72h only. In vivo, in animals receiving RT or AuNP only, CLR expression was increased relative to control animals and CLR was detected extracellularly after RT, and extra- and intracellularly after AuNP alone. However, after combined RT and AuNP, CLR expression was higher than after single treatments and was detected both, extra- and intracellularly. Conclusions: In BCa patients, induction of ICD may play a critical role in improving clinical outcomes. Here we show that AuNP enhanced the immunogenic effect of a single irradiation dose in BCa cells and mouse model. This effect was measured by an increase in the expression of CLR and HMGB1, DAMPs critical to the response of BCa. In addition, AuNP alone exhibited an immunogenic effect similar to RT alone. These findings support that BCa depends on ICD and provide a platform for designing multimodal BCa RT formulations with novel radiosensitizers or immunotherapy.

Public Health Sciences

Kalu R, Tang A, and Stefanou A. Pre-Hospital Admission Adversely Affects Outcomes after Colorectal Cancer Surgery: An Analysis of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Database. *Journal of the American College of Surgeons* 2020; 231(4):e107.

Introduction: Colorectal cancer is the third most common cancer in the US. Multiple factors such as age, sex, stage at diagnosis, tumor biology, invasiveness, and setting of surgery, have been shown to affect colon cancer outcomes even with optimal management. Patients usually undergo elective or emergent surgeries for colon malignancy while a significant proportion are admitted to the hospital beforehand. To our knowledge the effect of pre-hospital admission before colorectal surgery has not been previously reported. Using the National Surgical Quality Improvement Program (NSQIP) targeted colectomy database, we evaluated post-surgical outcomes of this patient population. Methods: The NSQIP database (2012-2017) was used to identify patients who underwent colon cancer resections and their preoperative admission status. Multivariate logistic regression weighted by inverse propensity score was performed to compare outcomes of the 2 groups. Results: A total of 9486 patients were evaluated, 50.1% males and 76% Caucasian. Preadmitted patients (12.9%) were significantly older, had multiple comorbidities, and more frequently had open operations. The preadmitted patients had a significantly longer total length of stay (15.9 vs 7.4 days), perioperative bleeding (20.3% vs 12.1%), and wound dehiscence (2.0% vs 1.1%). However, they had lower readmission rates (11.5% vs 14.3%, $p < 0.05$). There was no significant group difference in terms of rates of surgical site infection or reoperation. Conclusion: Compared to their counterparts preadmitted colorectal patients have a significantly longer LOS, bleeding complication, wound dehiscence, but a lower rate of readmission. Further study is needed to assess for long-term cancer-specific outcomes of these patients.

Public Health Sciences

Leonard-Murali S, Burmeister C, Susick L, Baker P, and Nathanson S. Where is It? Breast Cancer Location and Associations with Metastasis and Survival. *Journal of the American College of Surgeons* 2020; 231(4):e88-e89.

Introduction: Associations of primary breast cancer (BC) location on development of regional lymph node metastases (RLNM), distant metastases (DM), and mortality remain unclear. We aimed to characterize any associations, hypothesizing that upper-outer quadrant tumors would be associated with RLNM, DM, and reduced survival. Methods: Hormone-receptor positive, HER2-neu negative BC patients who underwent surgery (including RLN sampling) at a tertiary-care hospital system from 1995-2017 were prospectively reviewed. BC location was described as lower-inner quadrant (LIQ), lower-outer quadrant (LOQ), upper-inner quadrant (UIQ), upper-outer quadrant (UOQ), or central (C). Demographic and clinicopathologic variables were compared between location groups. Kaplan-Meier curves were constructed to analyze mortality by location. Multivariable logistic regression models were constructed to identify associations with RLNM or DM. Significance was established at $p < 0.05$. Results: 1822 patients met inclusion criteria. Location was most often UOQ, and least often C (C=65, 3.6%; LIQ=217, 11.9%; LOQ=244, 13.4%; UIQ=397, 21.8%; UOQ=899, 49.3%). There was no difference in RLNM between groups (C=15, 23.1%; LIQ=51, 23.5%; LOQ=61, 25.0%; UIQ=65, 16.4%; UOQ=204, 22.7%; $p = 0.057$), and no difference in DM between groups (C=3, 4.6%; LIQ=21, 9.8%; LOQ=14, 5.8%; UIQ=24, 6.1%;

UOQ=58, 6.5%; $p=0.351$). Kaplan-Meier curves showed no difference in survival between groups. By multivariable analysis, UIQ was associated with RLNM (reference group: UOQ; odds ratio=0.67, 95% confidence interval=0.47-0.94; $p=0.021$), with no other associations between location and RLNM or DM found. Conclusion: There were no consistent differences in RLNM, DM, or survival between BC locations. Location does not appear to be a prognostic factor in hormone-receptor positive, HER2-neu negative BC.

Public Health Sciences

Michaels AT, Peterson E, Luzum J, Gui H, Pinto Y, Sabbah HN, Williams LK, Snider J, and Lanfear DE. Biomarker Guided Therapy For Heart Failure With Mid-Range EF. *Journal of Cardiac Failure* 2020; 26(10):S37.

Background: Heart failure (HF) with mid-range ejection fraction (HFmrEF, EF 40-49%) accounts for ~15% of HF patients and these are a heterogeneous group with a phenotypic character that reflects aspects of both preserved and reduced EF HF. There are no proven treatments for this group but identifying subsets of patients that will respond to conventional therapies such as beta blockers (BB) would be desirable. We hypothesized that HFmrEF patients with elevated Nt-proBNP or ST2 would have more favorable response to BB therapy. Methods: A prospective registry was conducted that enrolled 1760 HF patients who met Framingham HF criterion and who received care through our health system and insurance product. Participants donated blood for biomarker measurements at enrollment and their medication exposure was quantified over time using pharmacy claims data. The current study utilized all participants who had EF 40-49% and baseline biomarker measurement ($n=338$). The primary endpoint was all-cause mortality. Biomarker categories were dichotomized at Nt-BNP >1000ng/L and ST2 ≥ 35 ng/mL. We quantified the HR for BB exposure overall and divided by biomarker level using Cox models adjusted for MAGGIC score and BB propensity score. Results: Vital status and Nt-BNP measurements were available for all 338 patients, while 279 had ST2 measured, and 201 had both markers (Table 1). For Nt-BNP, 200 (58%) had elevated levels while 143 (42%) had low values. BB use in patients with elevated Nt-BNP levels had a hazard ratio (HR) of 0.43 ($p=0.1$) compared to HR 0.97 ($p=0.97$) in the low Nt-BNP group. For ST2, 195 patients (70%) had levels <35 ng/mL while 84 (30%) had elevated levels. BB use in the elevated ST2 cohort had a HR 0.08 ($p=0.71$) vs. 0.62 ($p=0.72$) in the low ST2 group, a statistically significant interaction. ($p_{int}=0.089$). Both low marker groups had very low event rates (3.5% and 3.1% 1 year death, respectively). The combination of the two markers together (either elevated vs. both low) identified an especially low risk group with 1.5% dying and predicted the BB benefit association; in the low marker group BB HR =0.99 ($p >0.99$) while in patients with either ST2 or Nt-BNP elevated the BB HR was 0.06 ($p=0.03$). Conclusions: In this observational study of HFmrEF patients, those with low ST2 and Nt-BNP have low risk of death and little benefit of BB therapy whereas among the approximately two-thirds of patients with either marker elevated a substantial BB benefit association was seen

Public Health Sciences

Schaff E, Bergman D, Burmeister C, McHargue C, Lim H, and Siddiqui F. Impact of Gender and Race on Outcomes of Patients Treated for Mycosis Fungoides with Total Skin Electron Beam Therapy. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E47.

Background: Race and gender have been shown to affect patient outcomes in many different types of cancer. However, there is just one other paper which explores this in mycosis fungoides. Our institution is well suited for studying these disparities due to our diverse patient population. Objectives: To determine the impact of patient characteristics such as race and gender on the survival outcomes of patients with mycosis fungoides who have undergone total skin electron beam therapy as part of their treatment regimen. Methods: After IRB approval, 25 patients with mycosis fungoides who have undergone 26 courses of total skin electron beam therapy (TSEBT) were included in this analysis (one patient with 2 courses of TSEBT). These patients were treated between 2010 and 2019 with 36 Gy in 24 fractions over 8 weeks using the Stanford 6 technique. Data points were collected from all available medical records. Patients were stratified by race and by gender. Results: Patients were evenly distributed, with 13/25 African American (AA) vs 12/25 Caucasian, and 10/25 female vs 15/25 male. With a median follow up of 17 months (range 1-67 months), the progression free survival (PFS) at 6 months in African Americans vs Caucasians was 22% vs 39% ($p=0.25$) and at 1 year it was 7% vs 20% ($p=0.18$). When comparing by gender, the 6 month PFS for female vs male was 27% vs 33% ($p=0.95$) and at 1 year was 16% vs 11%

($p=0.96$). Overall survival (OS) at 1 year in AA vs Caucasians was 100% vs 73% ($p=N/A$) and at 2 years it was 71% vs 62% ($p=0.55$). When comparing by gender, the 1 year OS for female vs male was 89% vs 80% ($p=0.52$) and at 2 years it was 78% vs 53% ($p=0.35$). There were no significant differences in age, diagnosis to treatment time, previous treatment, or previous radiation therapy between the groups when comparing by race or by gender. Conclusions: To date there has been only one other paper addressing the factors of race and gender on the outcomes of TSEBT, and this paper had a relatively low percentage of AA patients (22%). In our study where the representation of AA patients is 52%, we confirmed that there is no significant difference in survival outcomes based on the patient's race. This was similarly observed in the comparison by gender as well. A major limitation of this study was the small sample size, as well as the retrospective nature of the analysis. Significantly, this study reinforces the point that in patients with Mycosis Fungoides, progression is almost inevitable and a multidisciplinary approach is the only effective means of management.

Public Health Sciences

Schaff E, Khalil R, Burmeister C, and Elshaikh M. External Beam Versus Brachytherapy as Adjuvant Radiation Therapy Modality in Patients with Stage II Endometrial Cancer: A Single Institution Experience. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E37.

Background: Current NCCN guidelines allow for the physician to choose between EBRT, brachytherapy, or a combination of both to treat FIGO stage II endometrial cancer. Physicians will typically choose the type of treatment based off of other risk factors such as grade, histology, size, depth of myometrial invasion, age, and presence of lymphovascular invasion. Henry Ford has a large database of patients who have been treated for endometrial cancer with adjuvant radiation following surgery and we sought to use this database to explore this area. Objectives: To determine the impact of adjuvant radiation treatment (RT) modality on overall survival (OS), recurrence-free survival (RFS), and disease-specific survival (DSS) in patients with FIGO stage II uterine endometrioid carcinoma (EC). Methods: Our prospectively-maintained database was queried for women with stage II uterine EC who underwent hysterectomy between 1990 and 2018. 100 patients were identified. None received adjuvant chemotherapy. OS, RFS, DSS were all calculated from the date of surgery by use of Kaplan-Meier analysis. Cox regression analysis was used to examine risks associated with changes in OS, RFS, or DSS. Results: The median follow-up time for the study cohort was 110.6 months, and the median age was 66 years. Lymphadenectomy was performed in 78%, peritoneal cytology in 85%. On pathology, 42% of patients were grade 1, 39% grade 2, and 19% grade 3. Adjuvant treatment was external beam radiation therapy (EBRT) alone in 15% of patients, HDR vaginal cuff brachytherapy (BT) alone in 29% and both in 56% of patients. 5-year RFS for the study cohort was 77%, DSS was 70% and OS was 70%. On multivariate analysis grade 3 vs 1 was a significant predictor for OS (HR 3.11, p 0.0228), RFS (HR 5.1, p 0.0333), but not DSS (HR 6.06, p 0.12). Radiation treatment modality (EBRT, BT, or both) were not found to be significant predictors for any of survival endpoint. Conclusions: In our group of stage II endometrial cancer patients adjuvant RT modality was not predictive of OS, RFS, or DSS. The only independent significant predictor in this group was grade 3 vs 1, and this was only significant for OS and RFS.

Pulmonary and Critical Care Medicine

Bagher-Ebadian H, Wu Q, Ghanem A, Brown S, Ajlouni M, Simoff M, Movsas B, and Chetty I. Radiomics Analysis and Unsupervised Self-Organizing-Map Technique to Predict Radiation-Induced Pneumonitis in Patients with Lung Cancer. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E49-E50.

Background: Lung radiation pneumonitis (RP) is one of the major toxicities experienced by lung cancer patients (13%–37%) receiving thoracic radiation therapy (RT) (Kocak Z, et al. *Int. J. Radiat. Oncol. Biol. Phys.* 2005 and Rodrigues G, et al. *Oncol.* 2004). Investigation of imaging biomarkers that can predict the incidence of RP can be useful toward reduce the probability of RP development. In this pilot study, we investigated the application of Kohonen Self-Organizing Map (K-SOM; a type of adaptive model that is trained using unsupervised competitive-learning (Kohonen T, Springer 1995)), for analysis of radiomic features extracted from normal lung tissue of non-RP and RP patients. The goal was to build an adaptive model to stratify patients and to reveal dominant characteristics of radiomics features for patient stratification. These characteristics are likely to remain unnoticed using conventional statistical analysis.

Objectives: To perform deep and unsupervised analysis of radiomics features extracted from planning CT images of normal lung tissue for patients with locally advanced, non-small cell lung cancers (NSCLC) to characterize and stratify patients with and without radiation-induced RP. Methods: Planning CT images of 41 patients (14 with RP and 27 with no evidence of RP) with stage-III lung cancers, treated with IMRT/3D-CRT, were studied. One hundred sixty eight radiomics features were extracted from the volume of normal lung tissue receiving ≥ 20 Gy, excluding the ITV, according to the following 8 different classes: Intensity Histogram Based Features (IHBF), Gray Level Run Length (GLRL), Law's Textural information (LAWS), Discrete Orthonormal Stockwell Transform (DOST), Local Binary Pattern (LBP), 2D-Wavelet Transform (2DWT), 2D-Gabor Filter (2DGF), and Gray Level Co-Occurrence Matrix (GLCM). A K-SOM ([9x9]-neurons) was constructed using 168 radiomic features and was trained and evaluated using random-permutation-sampling method (100-iterations, 67% and 33% for modeling and testing respectively). Regions pertaining to the dominant characteristics of the discriminant features were identified in the K-SOM space and used to calculate stratification power of the classifier. Results: The K-SOM revealed 3 dominant regions associated with the RP status: high-certainty-non-RP, high-certainty-RP, and intermediate/uncertain region. The average of AUC, positive predictive and negative predictive values were 76.20%, %71.65, and 82.12% respectively. Correlation-based dissimilarity analysis ($r < 0.2$, p -value < 0.05) ranked and revealed the stability and robustness of the 6 discriminant features as follows: Skewness, Entropy, and Moment (3 and 4) from IHBF, Entropy-CA1 from DOST, and Short-Run-Emphasis from GLRL. Conclusions: The results of this pilot study, albeit subject to confirmation in a larger patient population, suggest a potential role for the use of an unsupervised method for radiomics-based stratification and prediction of radiation-induced pneumonitis in patients with locally advanced NSCLC.

Radiation Oncology

Amini A, Verma V, Simone C, **Chetty I**, Choi JI, Chun S, Donington J, Edelman M, Higgins K, Kestin L, Mohindra P, **Movsas B**, Rodrigues G, Rosenzweig K, **Rybkin I**, Shepherd A, Slotman B, Wolf A, and Chang J. American Radium Society® (ARS) Appropriate Use Criteria on Radiation Therapy in Oligometastatic or Oligoprogressive Non-Small Cell Lung Cancer (NSCLC). *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E48.

Background: Recently, small randomized phase II studies have demonstrated significant improvements in progression free survival (PFS) and overall survival (OS) with the addition of stereotactic body radiation therapy (SBRT) in stage IV non-small cell lung cancer (NSCLC) patients with oligometastatic disease. Yet, current guidelines on local therapy for oligometastatic disease are lacking. Objectives: The American Radium Society (ARS) Appropriate Use Criteria Thoracic Panel was assigned to create guidelines on consolidative local therapy (radiotherapy, surgery, and others) recommendations for oligometastatic and oligoprogressive NSCLC patients. Methods: A panel of radiation, medical, and surgical oncologists at academic and private practices evaluated best practice based on the current available data on the following topics/scenarios: 1) defining oligometastasis and oligoprogression, 2) role of radiation in oligometastatic disease in the up-front setting, 3) role of consolidative radiation after stable/partial response following upfront systemic therapy, 4) management of the primary and N1-N3 nodal disease, 5) role of consolidative radiation for oligoprogression during systemic therapy, 6) role of consolidative radiation for cases with targetable driver mutations, and 7) management of brain metastases in the oligometastatic or oligoprogressive setting. Results: Based on current data and consensus by the expert panel, the optimal definition of oligometastatic and oligoprogression is ≤ 3 metastatic deposits, not including the primary tumor, with the understanding that ongoing trials may alter this threshold. In the scenario of radiation for oligometastatic disease in the up-front setting, several single-arm prospective trials support this approach and, therefore, this may be one feasible approach, although most contemporary randomized studies along with ongoing phase III trials are designed with standard of care systemic therapy in the upfront setting, followed by locally ablative therapy (LAT). Two randomized controlled phase 2 studies have demonstrated that the addition of local consolidative RT or surgery for oligometastatic NSCLC improved PFS and OS. Therefore, the panel supports the utilization of LAT as an option following upfront systemic therapy in oligometastatic patients. Thoracic nodal treatment is also discussed with various radiation approaches, including hypofractionation and SBRT. Prospective data on SBRT for oligoprogression are limited, but there is some suggestion that LAT may be beneficial in select patients. In patients with targetable mutations, a similar approach should be offered, although the consensus panel acknowledges a low sample size of these patients in existing trials. Lastly, the treatment

of brain metastases should be based on multiple factors including the number of metastases, patient symptoms, and presence of a molecular target. Conclusions: The guideline topics discussed here are the first in the management of oligometastatic and oligoprogressive NSCLC based on a multidisciplinary panel of physicians. Finalized recommendations from the committee will be presented at the annual ARS meeting.

Radiation Oncology

Anker C, **Dragovic J**, Abdel-Wahab M, Bianchi N, Goodman K, Herman J, Jones W, Kennedy T, Konski A, Kumar R, Lee P, Russo S, Sharma N, Small W, Suh W, Tchelebi L, and Jabbour S. American Radium Society (ARS) and American College of Radiology (ACR) Appropriate Use Criteria (AUC) Systematic Review and Guidelines for Operable Esophageal Adenocarcinoma. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E31.

Background: The ARS AUC are evidence-based guidelines that are reviewed by a multidisciplinary expert panel. Objectives: Our goal was to summarize the literature regarding outcomes following surgery alone as well as neoadjuvant, adjuvant, and definitive chemotherapy and/or radiation treatment strategies for the treatment of operable adenocarcinoma of the esophagus and gastroesophageal junction (GEJ). Methods: A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) systematic review assessed all studies within Ovid Medline, Embase, and Cochrane Central Databases published through 6/2019 evaluating toxicities, local control and/or overall survival (OS) for operable esophageal adenocarcinoma. Of 2786 abstracts screened, 77 full text articles were assessed for eligibility after which 45 remained after exclusions and formed the basis for our findings. Results: • Several meta-analyses have concluded that neoadjuvant chemoradiation (nCRT) is associated with significant improvements in OS and R0 resection rate compared to surgery alone. • Compared to neoadjuvant chemotherapy (nCT), nCRT significantly increased the incidence of locoregional control, pathologic complete response and R0 resection rate for esophageal/GEJ patients; however, this did not translate to an improvement in OS. In a meta-analysis of patients with esophageal cancer, the OS benefit found comparing nCT or peri-operative chemotherapy to surgery alone was lost on subset analysis for adenocarcinoma. • Although several meta-analyses have not found an increase in complications with nCRT, one network meta-analysis found a strong trend towards increased post-operative mortality with nCRT compared to either surgery alone or nCT. • In a meta-analysis of studies comparing definitive CRT (dCRT) vs. nCRT, OS was significantly lower for dCRT. However, when only analyzing studies with equal stage/performance status patients at baseline, no significant differences were found. However, small numbers of adenocarcinoma patients limits definitive conclusions. • For T2N0 patients, compared to surgery alone the addition of neoadjuvant radiation with or without chemotherapy was found to improve R0 resection rate but not OS; however, studies have demonstrated that over one third of patients are clinically understaged. • Adjuvant CRT following upfront surgery is controversial and interpretation is limited by small numbers of adenocarcinoma patients, and an OS benefit was only noted on subset analysis for those with positive lymph nodes. Conclusions: Although a number of meta-analyses comparing various treatment options for operable esophageal cancer exist, limited numbers of adenocarcinoma patients often hinder definitive conclusions. Optimum oncologic outcomes are most consistently described with nCRT except for early stage T2N0 patients, and the potential for increased post-operative mortality with nCRT should be acknowledged. ARS AUC committee recommendations will be presented.

Radiation Oncology

Bagher-Ebadian H, Wu Q, Ghanem A, Brown S, Ajlouni M, Simoff M, Movsas B, and Chetty I. Radiomics Analysis and Unsupervised Self-Organizing-Map Technique to Predict Radiation-Induced Pneumonitis in Patients with Lung Cancer. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E49-E50.

Background: Lung radiation pneumonitis (RP) is one of the major toxicities experienced by lung cancer patients (13%–37%) receiving thoracic radiation therapy (RT) (Kocak Z, et al. *Int. J. Radiat. Oncol. Biol. Phys.* 2005 and Rodrigues G, et al. *Oncol.* 2004). Investigation of imaging biomarkers that can predict the incidence of RP can be useful toward reduce the probability of RP development. In this pilot study, we investigated the application of Kohonen Self-Organizing Map (K-SOM; a type of adaptive model that is trained using unsupervised competitive-learning (Kohonen T, Springer 1995)), for analysis of radiomic

features extracted from normal lung tissue of non-RP and RP patients. The goal was to build an adaptive model to stratify patients and to reveal dominant characteristics of radiomics features for patient stratification. These characteristics are likely to remain unnoticed using conventional statistical analysis. Objectives: To perform deep and unsupervised analysis of radiomics features extracted from planning CT images of normal lung tissue for patients with locally advanced, non-small cell lung cancers (NSCLC) to characterize and stratify patients with and without radiation-induced RP. Methods: Planning CT images of 41 patients (14 with RP and 27 with no evidence of RP) with stage-III lung cancers, treated with IMRT/3D-CRT, were studied. One hundred sixty eight radiomics features were extracted from the volume of normal lung tissue receiving ≥ 20 Gy, excluding the ITV, according to the following 8 different classes: Intensity Histogram Based Features (IHBF), Gray Level Run Length (GLRL), Law's Textural information (LAWS), Discrete Orthonormal Stockwell Transform (DOST), Local Binary Pattern (LBP), 2D-Wavelet Transform (2DWT), 2D-Gabor Filter (2DGF), and Gray Level Co-Occurrence Matrix (GLCM). A K-SOM ([9x9]-neurons) was constructed using 168 radiomic features and was trained and evaluated using random-permutation-sampling method (100-iterations, 67% and 33% for modeling and testing respectively). Regions pertaining to the dominant characteristics of the discriminant features were identified in the K-SOM space and used to calculate stratification power of the classifier. Results: The K-SOM revealed 3 dominant regions associated with the RP status: high-certainty-non-RP, high-certainty-RP, and intermediate/uncertain region. The average of AUC, positive predictive and negative predictive values were 76.20%, 71.65%, and 82.12% respectively. Correlation-based dissimilarity analysis ($r < 0.2$, p -value < 0.05) ranked and revealed the stability and robustness of the 6 discriminant features as follows: Skewness, Entropy, and Moment (3 and 4) from IHBF, Entropy-CA1 from DOST, and Short-Run-Emphasis from GLRL. Conclusions: The results of this pilot study, albeit subject to confirmation in a larger patient population, suggest a potential role for the use of an unsupervised method for radiomics-based stratification and prediction of radiation-induced pneumonitis in patients with locally advanced NSCLC.

Radiation Oncology

Cook A, Khalil R, Burmeister C, and Elshaikh M. The Impact of Different Adjuvant Managements on Survival Endpoints in Women with Adequate Surgical Staging Early Stage Uterine Serous Carcinoma. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E36.

Background: Non-endometrioid carcinomas, which includes uterine serous carcinoma (USC), comprise only 15% of all endometrial carcinomas but cause about 40% of deaths in this patient population. The ideal adjuvant management of patients with early-stage USC is remains unknown. Objectives: To report survival outcomes in women with early stage USC after adequate surgical staging with various adjuvant management options. Methods: After IRB study approval, our prospectively-maintained database for women with endometrial carcinoma was queried for women with 2009 International Federation of Gynecology and Obstetrics (FIGO) stages I-II USC based on WHO pathologic definition who underwent adequate surgical staging between 1/1991 and 4/2017 followed by adjuvant management [surveillance, radiation treatment (RT) or chemotherapy (CT) or combination (CRT)]. Chi-squared tests were performed to compare differences in outcome by type of adjuvant management. Recurrence-free (RFS), disease-specific (DSS) and overall survival (OS) were assessed by Kaplan-Meier and log-rank tests. Univariate and multivariate analyses were performed to identify statistically significant predictors of survival endpoints. Results: We identified 155 women who met our inclusion criteria. The median follow-up time was 54.8 months. 75% of the study cohort were with stage IA, 14% stage IB and 11% with stage II. All women underwent pelvic lymph node dissection with a median number of dissected lymph nodes of 15. Omentectomy was performed in 62% of women. Adjuvant RT was utilized in 55% of women (54 with vaginal brachytherapy alone, 22 with pelvic RT and 10 with combination). Most commonly used chemotherapy was carboplatin and paclitaxel with a median number of cycles of 6. 5-year RFS was 78% for those received CRT, 84% for RT alone, 65% who received CT alone and 48% for those who were observed ($p=0.03$). 5-year DSS was 79%, 92%, 66% and 53%, respectively ($p=0.02$). 5-year OS was 76%, 79%, 63% and 53%, respectively ($p=0.21$). On multivariate analysis of OS, old age, and not receiving any adjuvant therapies were independent predictors of worse OS. Independent predictors of better RFS and DSS included adjuvant RT alone or with chemotherapy, and lack of lymphovascular space invasion. Conclusions: In this cohort of women with adequate surgical staging, adjuvant radiation treatment with or without chemotherapy is associated with reduced tumor recurrence with improved survival endpoints.

Radiation Oncology

Feldman A, Devpura S, Movsas B, Chetty I, Cook A, Rusu S, Brown S, Kim J, Sun Z, Ajlouni M, mayyas E, Liu J, Liu C, and Snell D. A Prospective Analysis of Quality of Life Data and Clinical Toxicity as a Function of Radiation Dose and Volume in Stage I Lung Cancer Patients after SBRT. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E64.

Background: Stereotactic body radiation therapy (SBRT) is an appropriate treatment option for patients with stage I non-small cell lung cancer (NSCLC) who are not surgical candidates. As these patients often present with significant co-morbidities, quality of life (QOL) outcomes are especially important. Objectives: To use a validated patient reported quality of life (QOL) assessment tool to measure clinical toxicity and patient reported quality of life (QOL) outcomes up to 36 months after SBRT in stage I NSCLC patients based on pre-treatment dosimetric parameters and tumor volumes. Methods: Fifty-six stage I NSCLC patients treated with SBRT (12 Gy x 4) were prospectively monitored for symptoms including cough, dyspnea, fatigue, and pneumonitis. Symptoms were measured at baseline (before treatment), immediately after treatment and 3, 6, 12, 18, 24, and 36 months post-treatment. Toxicity was graded from zero to five following the Charlson comorbidity and toxicity index. Quality of life was determined using the previously-validated Functional Assessment of Cancer Therapy-Trial Outcome Index (FACT-TOI) Lung questionnaire which incorporated three subscale endpoints: lung subscale (LSC), physical well-being (PWB) and functional well-being (FWB). Dosimetric parameters, including the mean lung radiation dose (MLD), and the volume of normal lung receiving at least 5, 10, 13 or 20 Gy (V5, V10, V13, and V20) were obtained from the treatment plan. Pearson correlation and student t-test analyses were used to measure correlations and distinguish between lung metrics with QOL and clinical toxicities. Results: SBRT produced minimal toxicities. QOL (TOI, LSC, PWB, or FWB) at 3, 6, 12 and 24 months post-treatment were significantly correlated with V5, V10, V13, V20, or MLD. Radiation pneumonitis showed mild positive but statistically significant ($P < 0.05$) correlation with V20. Moreover, FWB at 3 months showed mild negative correlation with dyspnea. Conclusions: Lung SBRT treatment for patients with NSCLC, using a 12 Gy x 4 dose regimen, was well tolerated with minimal toxicity observed. A validated patient related quality of life assessment tool was used to identify the dosimetric parameters most crucial for treatment planning. Further follow-up is recommended.

Radiation Oncology

Ghanem A, Schymick M, Khalil R, Williams A, and Siddiqui F. Does the use of Marijuana Impact Outcomes in Patients with Squamous Cell Carcinoma of the Oropharynx? *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E42.

Background: The incidence of human papilloma virus (HPV) associated oropharyngeal squamous cell carcinoma (OP-SCC) has increased significantly in the past few years. While many of these patients do not abuse tobacco products, they may use marijuana in various forms. The impact of marijuana use/abuse on survival and local control in head and neck cancer patients is not well understood. Objectives: The purpose of our analysis was to evaluate the management and outcomes in our patients treated for OP-SCC stratified according to marijuana use. Methods: After obtaining Institutional Review Board (IRB) we used our institutional database of 360 patients with detailed psychosocial and substance abuse history to identify patients with OP-SCC. Clinico-pathological data and treatment details were compared between marijuana users vs. non-users. Using Kaplan-Meier curves and log-rank test were evaluated overall (OS), disease free (DFS), distant metastases free (DMFS) and locoregional free (LRFS) survival based on Marijuana use. Results: We identified 74 patients with OP-SCC of which 62 (84%) were male, 55 (74%) were Caucasians and 52 (70%) were HPV+ve. Median age was 62 years (range: 41-71) and 61% were ever-smokers with median pack/year of 25.5. Radical surgery was undergone in 17 (23%), whereas, the rest 57 (77%) were treated by definitive chemoradiotherapy. Marijuana users encompassed 35% of the study cohort (n=26) and non-users were 65% (n=48). Clinicopathological details not differ between the study groups. In addition, marital status, highest educational level, alcohol use and smoking history were similar. Marijuana users underwent marginally less surgeries (11.5 vs 29.2%; $p=0.085$), had higher median pain score (7 vs. 6) and more mean weight loss during radiotherapy (22.2 vs 18.5 Lb.), albeit nothing was significant ($p>0.05$). Although LRFS ($p=0.12$) and DMFS ($p=0.48$) did not differ between users vs. non-users; marijuana use was marginally detrimental for DFS (1-year 69% vs. 77%

and 3-years: 27% vs. 70%; $p=0.051$) and was associated with significantly worse OS (1-year: 60% vs. 82% and 3-years: 30% vs. 73%; $p=0.005$). Conclusions: Marijuana use was not associated with disease specific features. Nevertheless, there seems to be a significant impact of the use of marijuana and the adherence to RT, quality of life, and overall survival. A more detailed analysis is underway to better understand the impact of various psycho-social factors on RT treatment tolerance.

Radiation Oncology

Ghanem A, Woody N, **Shymick M**, Geiger J, Tsai CJ, Dunlap N, Liu H, Burkey B, Lamarre E, Caudell J, Porceddu S, Lee N, Adelstein D, Koyfman S, and **Siddiqui F**. Does the Incorporation of Chemotherapy to Adjuvant Radiation Skew the Influence of Treatment Package Time in High-risk Oral Cavity Carcinoma? A Multi-institutional Collaborative Study. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E5.

Background: Treatment package time (TPT) defined as days elapsing from surgery to the end of adjuvant radiation therapy (RT) is known to impact outcomes in head and neck cancer patients receiving adjuvant RT alone. Objectives: We sought to explore the influence of adding concomitant chemotherapy to adjuvant RT (CRT) on the effect of TPT in high risk oral cavity squamous cell carcinoma (OCSCC). Methods: We queried our multi-institutional oral cavity collaborative database with 1282 cases to identify OCSCC diagnosed between 2005-2015 that received adjuvant CRT after surgery. All included cases had at least a high-risk feature (extracapsular nodal extension (ECE) and/or positive final surgical margin (PM)) and were treated within 180 days beyond surgery. TPT was calculated in days between surgery date and the last RT fraction and was stratified in 10 days increments (10D-INC). Kaplan-Meier curves, log-rank p-values and uni/multi-variate analyses (MVA) were used to investigate the interaction between TPT in 10D-INC and Overall (OS), locoregional failure free (LRFS) and distant metastases free (DMFS) survival. Results: We identified 187 cases treated with CRT who met out inclusion criteria after excluding cases with inadequate RT and those with unknown treatment dates. Median age was 58 years (24-87), males were 66% and ever smokers were 69% with median smoking pack years of 30. ECE and PM were detected in 32% and 85% respectively; and oral tongue then floor of mouth constituted 49% and 18% of the study cohort. Median RT dose delivered was 66 Gy and median cisplatin dose received was 200 mg/m² per patient. For the entire cohort median TPT was 98 days (63-162) divided between time to start RT of 51 days (29-109) and median total RT duration of 45 days (33-97). Two- and 5-years OS were significantly better for TPT \leq 90 days (28%) than TPT $>$ 90 days of 71% vs. 65% (2-years) and 62% vs. 45% (5-years); $p=0.05$ respectively. However, there was no difference for LRFS or DMFS ($p>0.05$). Clinico-pathological features, smoking index as well as RT and cisplatin doses were non-different between TPT \leq 90 vs. $>$ 90 days; nevertheless, more extensive lymph node (LN) dissection ($p=0.039$) and unplanned reoperation ($p=0.037$) were associated with TPT $>$ 90 days. On MVA, TPT in 10D-INC was independently detrimental for OS (HR:1.14; CI [1-1.28]; $p=0.043$) in addition to perineural invasion, age and positive LN ($p<0.05$ for all). Conclusions: TPT was associated with worsened OS in one of the largest multi-institutional cohorts treated with modern modalities with no influence on LRFS or DMFS for high-risk OCSCC managed with adjuvant CRT. The addition of concurrent chemotherapy to adjuvant RT is suggested to negate the established impact of TPT on oncologic outcomes. Worse OS with prolonged TPT seemed to be driven by peri-operative complications and poor performance status.

Radiation Oncology

Ghanem A, **Zhu S**, **Morris E**, **Movsas B**, **Chetty I**, and **Glide-Hurst C**. Quantification of Cardiac Substructure Inter-fraction Displacement for MR-guided Radiation Therapy. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E17-E18.

Background: Radiation therapy (RT) dose to cardiac substructures has been linked to toxicities including coronary heart disease and heart failure. However, cardiac substructures are poorly visualized on traditional non-contrast treatment planning computed tomography (CT) images due to limited soft tissue contrast. Objectives: We sought to quantify inter-fraction displacements of cardiac substructures using daily magnetic resonance (MR) guided RT datasets that can be applied for robust per-structure margin design. Methods: Nine cases with 11 non-breast lesions in the thoracic region [lung, mediastinum, and esophagus] were retrospectively analyzed. All patients underwent daily MR-guided RT using a 0.35T MR-linac (6 end-inhale, 2 end-exhale using a 17-25 s TrueFISP scan, 1.5 \times 1.5 \times 3 mm³ resolution, 1 free

breathing (~3-minute TrueFISP scan, resolution= 1.5x1.5x1.5 mm³). To elucidate cardiac substructures, MR datasets (0.35T) for simulation (MR-SIM) and treatment fractions at the same breath-hold position were rigidly co-registered to the planning CT using bony alignment. A hybrid diagnostic MR/CT atlas was used to propagate contours for 12 cardiac substructures (e.g. chambers, coronary arteries (CA), and great vessels) to all serial MR-SIM and 3-4 fractions for each case (n=35) that were then modified by two radiation oncologists as needed. After performing a tumor-based image registration to the initial MR-SIM, inter-fraction differences were quantified via centroid analysis. Dominant axes of displacement were identified for each substructure. Results: Over all fractions, the average inter-fraction shift of the heart from the MR-SIM was 2.3 ± 1.5 mm, 1.7 ± 1.6 mm and 2.9 ± 2.2 mm in the left-right (L-R), anterior-posterior (A-P), and superior-inferior (S-I) directions, respectively with an overall vector displacement of 4.6 ± 2.3 mm. In the L-R direction, the left atrium had the lowest mean shift (2.2 ± 1.8 mm) with the heart chambers ranging between 2.7 - 3.1 ± 2 mm. Great vessels (i.e., ascending aorta, superior vena cava and pulmonary vein) with a shift of 1.7 ± 1.2 mm had the minimal displacement across fractions in the A-P axis; whereas the right ventricle shifted the least (2.6 ± 2 mm) followed by other heart chambers (3.1 ± 2 mm) in the S-I direction. The maximum inter-fraction vector displacement occurred for the left anterior descending (8.7 ± 4.2 mm), left main (6.9 ± 2.5 mm) and right (6.8 ± 2.8 mm) CA. For two patient fractions, SI deviations were >1 cm for most substructures due to lack of compliance with breath-hold conditions. Conclusions: Cardiac substructure displacements demonstrated variability in magnitude and dominant axis, suggesting that anisotropic substructure-specific planning organ at risk margins may be warranted. While these results suggest patient-specific margins may be necessary, more precise margin definition requires confirmation in a larger cohort and accounting for other uncertainties.

Radiation Oncology

Harris E, **Walker E**, and Chadha M. Management of Regional Nodes in the Treatment of Breast Cancer: An American Radium Society Appropriate Us Criteria Panel for Breast Cancer Systematic Review and Guideline. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E15-E16.

Background: The management of regional nodes in breast cancer patients is a complex and evolving area of significant clinical impact. Numerous recent randomized trials and other studies have reported improved survival outcomes associated with the inclusion of regional nodal irradiation in patients with node positive breast cancer or even high risk node negative breast cancer. The selection of patients for extent of axillary surgery has also been the subject of numerous randomized trials with a resulting reduction in the use of axillary dissection in many populations. Selection of systemic agent sis increasingly driven by molecular assays rather than clinicopathologic features such as number of positive nodes. Treatment of nodal volumes can also increase chronic toxicities such as lymphedema and reduced range of motion, so would ideally be used in patients who truly benefit. Many controversies remain, including optimal patient selection in the intermediate risk patients especially after mastectomy and after neoadjuvant chemotherapy, which nodal volumes to include in which patients, and the optimal dose fractionation. Several ongoing randomized trials are examining the role of nodal treatment after neoadjuvant chemotherapy and dosing regimens. Objectives: Due to the emerging body of data and the evolving standards, the ARS Breast Cancer AUC panel has launched a new topic on the management of regional nodes in breast cancer treatment. Our goal is to provide guidance for the multidisciplinary decision making regarding extent of surgery, use of nodal radiation and selection of sequencing of systemic agents as indicated by molecular subtyping and other genomic assays. Methods: A systematic literature review of the randomized controlled trials, meta-analyses and other prospective or population based studies was conducted to identify the studies published since January 2000. An evidence table was developed and studies ranked by study type, findings and level of evidence. Results: Topics for evidence-based guideline development include use of sentinel node lymphadenectomy for pathologic node negative and selection of patients for further axillary dissection with positive sentinel nodes, regional nodal irradiation instead of axillary dissection, regional node irradiation after neoadjuvant chemotherapy, design of radiation treatment parameters including target volumes, radiation fields and techniques and impact of genomic assays on selection of therapy. A review article and executive summary along with variants of clinical scenarios is under development to provide a guideline to clinicians regarding these patient populations. Variants are scored by consensus mythology to provide strength of evidence and consensus. Conclusions: The management of lymph nodes in early stage breast cancer patients at intermediate risk for recurrence involves several areas of controversy and evolving practice which this

evidence-based appropriate use criteria project addresses in order to provide practical guidance to the multidisciplinary oncology community.

Radiation Oncology

Janic B, Brown S, Neff R, Liu F, Bobbitt K, Mao G, Chetty I, Movsas B, and Wen N. Radiation and Gold Nanoparticle Increase the Expression of Immunogenic Cell Death Markers in MDA MB 231 Breast Cancer Model. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E26-E27.

Background: Tumor immunogenic cell death (ICD) plays a major role in stimulating host anti-cancer immune response that can determine the success of cancer radiotherapy (RT). Additionally, ICD can also be induced by radiation itself. The main feature of ICD is the release of immunogenic molecules by dying cells, termed damage associated molecular patterns (DAMPs) that act on innate and adaptive immune components to induce long-lasting antitumor immunity. Two breast cancer (BCa) DAMPs involved in phagocytosis and dendritic cell antigen presentation are Calreticulin (CLR) and HMGB1; loss of HMGB1 expression is linked to poor clinical prognosis. Therefore, these molecules are being studied for their therapeutic and prognostic potential. As RT, either alone or in combination, is often part of standard BCa therapies, the effect of RT and radiosensitizers, such as gold nanoparticles (AuNPs), on DAMPs expression must be considered when designing new protocols, especially if combining RT with an adjuvant mode such as immunotherapy. Objectives: The goal of this study was to measure the effect of radiation on CLR and HMGB-1 expression in the presence and absence of a novel AuNP radiosensitizer in MDA MB 231 BCa in vitro and in vivo models. We hypothesized that AuNP modulates radiation induced ICD by altering CLR and HMGB1 expression. Methods: In vitro: MDA MB 231 cells were incubated for 3h with 14nm AuNPs and irradiated. After 48h and 72h the percentages of CLR and HMGB1 positive cells were determined by flow cytometry. In vivo: Female nude mice bearing MDA MB 231 tumors received intratumoral injections of 14 nm AuNPs. After 24h mice were irradiated with 15 Gy dose using 160 kV photons. Mice were euthanized, histological sections prepared, stained with anti CLR antibodies and analyzed by light microscopy. Results: In vitro, radiation induced increase in the percentages of CLR and HMGB1 positive cells was potentiated by AuNP at 48h and 72h time points. In control cells, AuNP alone increased the percent of HMGB1 positive cells at both time points. The percent of CLR positive cells was increased at 72h only. In vivo, in animals receiving RT or AuNP only, CLR expression was increased relative to control animals and CLR was detected extracellularly after RT, and extra- and intracellularly after AuNP alone. However, after combined RT and AuNP, CLR expression was higher than after single treatments and was detected both, extra- and intracellularly. Conclusions: In BCa patients, induction of ICD may play a critical role in improving clinical outcomes. Here we show that AuNP enhanced the immunogenic effect of a single irradiation dose in BCa cells and mouse model. This effect was measured by an increase in the expression of CLR and HMGB1, DAMPs critical to the response of BCa. In addition, AuNP alone exhibited an immunogenic effect similar to RT alone. These findings support that BCa depends on ICD and provide a platform for designing multimodal BCa RT formulations with novel radiosensitizers or immunotherapy.

Radiation Oncology

Liu Y, **Venkatesulu BP**, Sharma A, Pollard-Larkin JM, Sadagopan R, Symons J, Neri S, Singh P, Tailor R, Lin S, and Krishnan S. High Dose Rate Radiation does not Protect Normal Tissue in Mice Cardiac and Splenic Models of Lymphopenia and Gastrointestinal Mucosal Injury. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E24.

Background: High dose rate radiation, also known as FLASH, is delivery of radiation at rates that far exceed conventional radiation (35-100 Gy/s vs 1-4 Gy/min). This approach has shown promise in recent preclinical studies demonstrating that not only does it have equivalent therapeutic efficacy as conventional radiation, but it may also lead to reduced toxicity to certain normal tissues (Favaudon V, et al. *Sci Transl Med* 2014, Vozenin M, et al. *Clin Cancer Res* 2019, Montay-Gruel P, et al. *Radiother Oncol* 2017). However, our understanding of the types of normal tissue that have improved sparing by FLASH is incomplete. Objectives: In this study, we first aimed to compare the tumoricidal efficacy of FLASH to conventional radiation. Additionally, we addressed whether FLASH can lead to reduced lymphopenia and/or gastrointestinal mucosal injury compared to conventional radiation. Methods: FLASH radiation was delivered at 35 Gy/s. Tumoricidal efficacy was assessed in vitro using clonogenic assays with 2 murine

pancreatic cell lines, KPC and Panc02, treated with 0-8 Gy of conventional or FLASH radiation. To address lymphopenia ex vivo, human peripheral blood mononuclear cells (PBMCs) were irradiated with 2 Gy of conventional or FLASH radiation and apoptosis and necrosis were assessed at 24h and 72h with flow cytometry. To assess lymphopenia in vivo, mice were exposed to conventional or FLASH radiation to the heart (2 Gy/day x 5 days or 10 Gy x 1) or spleen (1 Gy/day x 5 days or 5 Gy x 1) and levels of CD3, CD4, CD8, and CD19 cells were assessed at 3, 10, 17, and 24 days. Lastly, to assess GI mucosal toxicity in vivo, mice were exposed to a single 16Gy dose to the abdomen with conventional or FLASH radiation and survival was assessed. Results: FLASH was approximately 30% more effective in killing mouse pancreatic cell lines compared to conventional radiation. FLASH did not lead to improved sparing of ex vivo human PBMCs compared to conventional radiation with a similar profile of early apoptotic, late apoptotic, and necrotic cells. Mice exposed to FLASH radiation to the heart or spleen had more severe depletion and slower recovery of lymphocytes compared to conventional radiation. Mice exposed to total abdominal radiation with FLASH had worse overall survival compared to mice treated with conventional radiation. All mice died within 7 days of FLASH compared to mice surviving up to 15 days after conventional radiation. Conclusions: Our study confirms previous reports showing that FLASH is non-inferior to conventional radiation in tumoricidal efficacy and may actually be more effective. However, unlike previous studies, we found that FLASH had worse toxicity in the setting of lymphopenia and GI mucosa, which suggests that the advantages of FLASH may be tissue and/or dose dependent. The optimal regimen of FLASH and the mechanistic basis of its improved or worsened sparing of normal tissues remain important issues to be addressed.

Radiation Oncology

Margalit D, Sacco A, Bakst R, Beadle B, Beitler J, **Chang S**, Chen A, Cooper J, Galloway T, Koefman S, Ridge J, Robbins J, Truong MT, Tsai CJ, Yom S, and **Siddiqui F**. Postoperative Therapy for Resected Squamous Cell Carcinoma of the Head and Neck (SCCHN): Initial Findings of an American Radium Society (TM) (ARS) Appropriate Use Criteria Systematic Review (SR). *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E44.

Background: Progress in SCCHN management requires re-evaluation of postoperative therapy for resected SCCHN. Since the ARS and American College of Radiology (ACR) published a literature review and expert consensus guideline on postoperative therapy in 2011, additional relevant clinical trials have been published. Objectives: To comprehensively evaluate existing prospective clinical studies of postoperative therapy for resected SCCHN using a formalized methodologic approach described by the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Protocol, and to identify areas of accepted recommendations, controversy and uncertainty. Methods: The methodologic protocol for this SR was guided by PRISMA. Ovid Medline and Embase were searched on 01/10/2019 using medical subject headings designed to capture all published studies of HN cancer and postoperative therapy. The PICO (participants, interventions, comparators, outcomes) framework was used to identify published randomized trials, single and multi-arm non-randomized prospective clinical trials, and SRs/meta-analyses that adhered to a published methodology. Longitudinal prospective cohort studies were included if there was a baseline pre-intervention assessment. Excluded studies had <20 patients, were in non-English languages, or were case reports, case series, retrospective studies, large database studies, abstracts, preliminary analyses, narrative reviews, modeling studies, cell-line or non-clinical/non-human studies. Articles were selected if the population included adult patients with stage I-IVB SCCHN and no prior HN radiation who were treated with curative-intent surgery. Included disease sites were: oral cavity, oropharynx, hypopharynx, and larynx. The interventions of interest were postoperative radiation therapy (PORT), chemo-PORT, or postoperative chemotherapy, biologic therapy, targeted therapy, and/or immunotherapy. Studies were selected using Covidence® software by two independent reviewers based on study relevance related to the inclusion/exclusion criteria. Each study was graded using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence Table. Results: A total of 5,689 studies were identified. After removal of duplicates, 5,660 studies were screened using the title and abstract, leading to 201 studies assessed for relevance using full-text review. After limitation to the eligibility criteria, 96 studies were identified. An additional 4 eligible studies were added that were published after the cut-off date or were not identified through the literature search. Studies with primary oncologic endpoints included 11 SRs, 24 randomized trials, 28 non-randomized trials, and 9 post-hoc analyses of randomized trials. Studies of non-oncologic endpoints included 2 SRs, 1 randomized trial,

and 21 non-randomized clinical trials. Conclusions: This comprehensive, rigorously conducted SR identified 96 published prospective studies of postoperative therapy for SCCHN that constitute the evidence base for the ARS AUC HN Committee's systematic review. Recommendations and identification of areas of continuing disagreement requiring further research will be generated from this evidence base; these will be described in more detail at the time of presentation.

Radiation Oncology

Novick K, Chadha M, Harris E, Daroui P, Freedman G, Gao W, Hunt K, Park C, Rewari A, Suh W, **Walker E**, and Wong J. Utility of Bolus in Post Mastectomy Radiation. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E25-E26.

Background: The most common site of local recurrence after mastectomy is within skin and subcutaneous tissues anterior to the pectoralis muscles. The application of tissue-equivalent bolus can improve dose to the skin, which is often significantly below prescription dose in modern radiation treatment plans. However, practice surveys have shown a great degree of international heterogeneity in use of bolus (Vu 2007). Objectives: The American Radium Society (R) Appropriate Use Criteria (TM) Breast Cancer Committee examined the evidence for use of bolus in post mastectomy radiation. Methods: A PRISMA systematic review of available evidence through June 2019 was performed. The Committee reached a Delphi consensus on the appropriateness of bolus use in 3 different clinical variants. Results: Of 26 articles identified using the search terms, 18 were included as evidence. No randomized data for the effect of bolus application on local recurrence for modern photon treatment plans has been published. Several comparative retrospective studies show equivalent rates of recurrence with or without bolus (Abel 2017; Tieu 2011; Uematsu 1993; Turner 2016). Low rates of recurrence (4%-9%) and low rates of grade 2 acute dermatitis (9-10%) were reported without bolus. Probability of grade 2 dermatitis increased with Dmax greater than 5311 cGy (Shiba 2018). Dosimetric evaluation suggests that adequate dose to the skin can be achieved with application of 1 cm bolus in 15 out of 25 treatment days (Andic 2009). Alternatively, 2 mm brass mesh bolus could be applied daily, necessitating only one treatment plan (Ordonez-Sanz 2014; Manager 2016), but, due to risk of neutron formation, should not be used with higher energy photon beams (>10 MV). The Delphi consensus revealed that application of bolus to the chest wall was considered usually appropriate but the omission of bolus from cases involving reconstruction may be appropriate. There was a significant amount of the heterogeneity in the rating of appropriateness for the omission of bolus. Conclusions: Bolus use should be customized to the patient's skin dose and the patient's risk of skin recurrence. Some patients may have acceptable skin dose in their PMRT plan without bolus, so treatment plans with and without bolus should be evaluated. Patients with inflammatory carcinoma, positive anterior skin margins or poor skin dose without bolus may benefit more from more aggressive use of bolus while patients with breast reconstruction or poor skin healing may be at greater risk of toxicity with bolus. Aggressive use of bolus may include 1 cm bolus every other day or ≤0.5 cm daily. Less aggressive bolus may use 0.5 cm bolus every other day or no bolus. Removal of bolus after appearance of grade 2 acute dermatitis may help prevent progression to grade 3 toxicity and prevent treatment interruptions. Additional randomized evidence is greatly needed to resolve noted international and Committee heterogeneity regarding bolus use.

Radiation Oncology

Novick K, Chadha M, Harris E, Daroui P, Freedman G, Gao W, Hunt K, Park C, Rewari A, Suh W, **Walker E**, and Wong J. Hypofractionation of Post Mastectomy Radiation. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E25.

Background: The dose delivered to the chest wall is usually 50-50.4 Gy in 1.8-2 Gy daily fractions. The original studies for hypofractionation in breast cancer included a limited number of patients treated with mastectomy, but most did not have treatment of regional nodal volumes. As familiarity with hypofractionation of radiation to the intact breast has increased, there is a growing interest in use of hypofractionation of post mastectomy radiation. Objectives: The American Radium Society (R) Appropriate Use Criteria (TM) Breast Cancer Committee examined the evidence for the use of hypofractionation in post mastectomy radiation. Methods: A PRISMA search was conducted to find available evidence for hypofractionation of post mastectomy radiation. The Committee then reached a Delphi consensus for the use of hypofractionation for post mastectomy radiation in 2 clinical variants.

Results: Randomized studies of hypofractionated PMRT show lower levels of acute toxicity and similar outcomes, albeit with more limited follow up (Wang 2019, Zhao 2016, Versmessen 2012, Shahid 2009, Van Parijis 2012). A phase III study from China randomizing 820 high-risk patients to conventional (50 Gy in 25 fractions) versus hypofractionated radiation (43.5 Gy in 15 fractions) has reported non-inferiority at 5 years of follow up in respect of LRF and improvements in acute grade 3 skin toxicity (Wang 2019). All patients had treatment of the chest wall, level III axilla and supraclavicular fossa. Most patients received treatment to the chest wall using 6 MeV electrons using 2-dimensional treatment planning. Acute grade 3 skin toxicity was 3% in the hypofractionated group and 8% in the conventional fractionated group ($p < 0.0001$). A randomized trial by Van Parijis (2012) showed similar heart function and pulmonary function between conventional radiation and hypofractionated radiation. Grade 1 skin toxicity was improved with hypofractionation (60% versus 30%). Quality of life was likewise improved for patients with hypofractionated treatment in a randomized trial by Versmessen et al (2012). Shahid et al (2009) randomized 300 patients to 27 Gy in 5 fractions, 35 Gy in 10 fractions and 40 Gy in 15 fractions. Local control and toxicity were similar in all three schedules. The Alliance for Clinical Trials in Oncology is currently investigating with a phase III study of 880 participants the effect of a hypofractionated regimen of PMRT on patients who have breast reconstruction. A prospective phase II study of hypofractionated radiation to the postmastectomy chest wall and regional lymph nodes followed by a scar boost for a total of 49.95 Gy in 15 fractions found no grade 3 toxicities, but 29% reconstructive complications (Khan 2017). The Delphi consensus reported a median rating of 4 with high level of agreement, indicating that use of hypofractionation in post mastectomy radiation may be appropriate, particularly in the setting of a clinical trial. Conclusions: Although interest in hypofractionated treatment for PMRT is growing, additional follow up is necessary to determine the long-term safety and efficacy before generalized use. However, it may be appropriate outside the context of a clinical trial for patients without reconstruction if conventional fractionation is not available or is clinically challenging.

Radiation Oncology

Schaff E, Bergman D, Burmeister C, McHargue C, Lim H, and Siddiqui F. Impact of Gender and Race on Outcomes of Patients Treated for Mycosis Fungoides with Total Skin Electron Beam Therapy. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E47.

Background: Race and gender have been shown to affect patient outcomes in many different types of cancer. However, there is just one other paper which explores this in mycosis fungoides. Our institution is well suited for studying these disparities due to our diverse patient population. Objectives: To determine the impact of patient characteristics such as race and gender on the survival outcomes of patients with mycosis fungoides who have undergone total skin electron beam therapy as part of their treatment regimen. Methods: After IRB approval, 25 patients with mycosis fungoides who have undergone 26 courses of total skin electron beam therapy (TSEBT) were included in this analysis (one patient with 2 courses of TSEBT). These patients were treated between 2010 and 2019 with 36 Gy in 24 fractions over 8 weeks using the Stanford 6 technique. Data points were collected from all available medical records. Patients were stratified by race and by gender. Results: Patients were evenly distributed, with 13/25 African American (AA) vs 12/25 Caucasian, and 10/25 female vs 15/25 male. With a median follow up of 17 months (range 1-67 months), the progression free survival (PFS) at 6 months in African Americans vs Caucasians was 22% vs 39% ($p=0.25$) and at 1 year it was 7% vs 20% ($p=0.18$). When comparing by gender, the 6 month PFS for female vs male was 27% vs 33% ($p=0.95$) and at 1 year was 16% vs 11% ($p=0.96$). Overall survival (OS) at 1 year in AA vs Caucasians was 100% vs 73% ($p=N/A$) and at 2 years it was 71% vs 62% ($p=0.55$). When comparing by gender, the 1 year OS for female vs male was 89% vs 80% ($p=0.52$) and at 2 years it was 78% vs 53% ($p=0.35$). There were no significant differences in age, diagnosis to treatment time, previous treatment, or previous radiation therapy between the groups when comparing by race or by gender. Conclusions: To date there has been only one other paper addressing the factors of race and gender on the outcomes of TSEBT, and this paper had a relatively low percentage of AA patients (22%). In our study where the representation of AA patients is 52%, we confirmed that there is no significant difference in survival outcomes based on the patient's race. This was similarly observed in the comparison by gender as well. A major limitation of this study was the small sample size, as well as the retrospective nature of the analysis. Significantly, this study reinforces the point that in patients with Mycosis Fungoides, progression is almost inevitable and a multidisciplinary approach is the only effective means of management.

Radiation Oncology

Schaff E, Khalil R, Burmeister C, and Elshaikh M. External Beam Versus Brachytherapy as Adjuvant Radiation Therapy Modality in Patients with Stage II Endometrial Cancer: A Single Institution Experience. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E37.

Background: Current NCCN guidelines allow for the physician to choose between EBRT, brachytherapy, or a combination of both to treat FIGO stage II endometrial cancer. Physicians will typically choose the type of treatment based off of other risk factors such as grade, histology, size, depth of myometrial invasion, age, and presence of lymphovascular invasion. Henry Ford has a large database of patients who have been treated for endometrial cancer with adjuvant radiation following surgery and we sought to use this database to explore this area. Objectives: To determine the impact of adjuvant radiation treatment (RT) modality on overall survival (OS), recurrence-free survival (RFS), and disease-specific survival (DSS) in patients with FIGO stage II uterine endometrioid carcinoma (EC). Methods: Our prospectively-maintained database was queried for women with stage II uterine EC who underwent hysterectomy between 1990 and 2018. 100 patients were identified. None received adjuvant chemotherapy. OS, RFS, DSS were all calculated from the date of surgery by use of Kaplan-Meier analysis. Cox regression analysis was used to examine risks associated with changes in OS, RFS, or DSS. Results: The median follow-up time for the study cohort was 110.6 months, and the median age was 66 years. Lymphadenectomy was performed in 78%, peritoneal cytology in 85%. On pathology, 42% of patients were grade 1, 39% grade 2, and 19% grade 3. Adjuvant treatment was external beam radiation therapy (EBRT) alone in 15% of patients, HDR vaginal cuff brachytherapy (BT) alone in 29% and both in 56% of patients. 5-year RFS for the study cohort was 77%, DSS was and OS was 70%. On multivariate analysis grade 3 vs 1 was a significant predictor for OS (HR 3.11, p 0.0228), RFS (HR 5.1, p 0.0333), but not DSS (HR 6.06, p 0.12). Radiation treatment modality (EBRT, BT, or both) were not found to be significant predictors for any of survival endpoint. Conclusions: In our group of stage II endometrial cancer patients adjuvant RT modality was not predictive of OS, RFS, or DSS. The only independent significant predictor in this group was grade 3 vs 1, and this was only significant for OS and RFS.

Radiation Oncology

Simone C, Amini A, **Chetty I**, Choi JI, Chun S, Donington J, Edelman M, Higgins K, Kestin L, Mohindra P, **Movsas B**, Rodrigues G, Rosenzweig K, Rybkin I, Shepherd A, Slotman B, Wolf A, and Chang J. American Radium Society (ARS) and American College of Radiology (ACR) Appropriate Use Criteria Systematic Review and Guidelines on Reirradiation for Non-small Cell Lung Cancer (NSCLC). *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E48-E49.

Background: Reirradiation (reRT) for locoregional recurrences can provide durable control and improved symptoms and progression-free survival for select NSCLC patients. Thoracic reRT, however, is particularly challenging due to its considerable risk and the current lack of standardized approaches, guidelines and dose constraints. To date, no systematic review on the safety and efficacy of reRT for NSCLC exists, and no dedicated guidelines are available. Objectives: This ARS-ACR Appropriate Use Criteria Systematic Review and Guidelines on Reirradiation for NSCLC provides direct guidance on the safety and efficacy of reRT and recommends consensus dose constraints for thoracic reRT to minimize risks of high grade toxicities. Methods: A PRISMA systematic review assessed all studies published through 3/2019 evaluating toxicities, local control and/or overall survival for NSCLC thoracic reRT. Of 236 articles, 49 remained after exclusions (3 prospective) and formed the basis for these recommendations on: 1) the role of concurrent chemotherapy with reRT, 2) factors associated with toxicity from reRT and 3) what reRT modalities, dose-fractionation schemas and dose rates should be used. Composite dose constraints were also recommended. Results: The available data suggest potential benefit in clinical outcomes with concurrent chemoradiation for reRT, but the decision should be based on patient performance status, tolerance to prior systemic therapy and other individual patient/tumor characteristics. There are no data to guide the use of concurrent targeted therapy or immunotherapy with reRT, and this is not recommended outside of a clinical trial. Acute esophagitis and pneumonitis and late pulmonary, cardiac/great vessel, esophageal, brachial plexus and spinal toxicities are dose limiting for reRT. Limited data exist regarding the use of hyperfractionation and low- or high-dose rate reRT for NSCLC. For conventionally fractionated reRT, intensity-modulated radiation therapy (IMRT) is recommended over 3D

conformal radiation therapy (3DCRT) to increase dose conformality. Particle therapy may further reduce toxicities and/or enable safer reRT dose escalation compared with 3DCRT and IMRT. Stereotactic body radiation therapy (SBRT) can provide increased conformality and dose escalation and is optimal for primary-alone failures, but caution is needed for central reRT with SBRT. Recommended reRT composite dose constraints in 2 Gy equivalent dose are: esophagus V60 <40% and DMax <100-110 Gy, lung V20 <40%, heart V40 <50%, aorta/great vessels DMax <120 Gy, trachea and proximal bronchial tree DMax <110 Gy, spinal cord DMax <57 Gy, and brachial plexus DMax <85 Gy. Conclusions: For the first time, consensus dose constraints for thoracic reRT are recommended to minimize the risks of high-grade and potentially fatal toxicities from repeat radiotherapy. Additional prospective data are needed, and toxicities should be correlated with reRT course and composite dose constraints.

Radiation Oncology

Tsai CJ, Galloway T, Beitler J, Cooper J, Bakst R, Ridge J, Beadle B, Robbins J, Chen A, Sacco A, **Chang S**, Truong M, Koyfman S, Yom S, and **Siddiqui F**. Ipsilateral Radiation for Squamous Cell Carcinoma of the Tonsil: Summary of Findings and Controversies from the ARS Appropriate Use Criteria Expert Panel on Tonsil Cancer. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E41-E42.

Background: In 2012 the American College of Radiology (ACR) published the Appropriateness Criteria for Ipsilateral Radiation for squamous cell carcinoma (SCC) of the tonsil. Since then there have been additional advancements and publications pertinent to this topic. Objectives: We performed an updated literature review and summarize the findings as well as potential controversies. Methods: We performed a PubMed search of articles published between January 2000 and June 2019 using various combinations of 25 pre-determined keywords and restricted to articles having the full text available, written in the English language, and on human subjects. Of the 46 citations returned from the search, the authors added 3 citations from bibliographies, websites or books not found in this literature search. Of the 49 citations, 30 citations were retained for further detailed review, and 14 of them were added to the evidence table. Articles were removed from the bibliography if they were not relevant or generalizable to the topic, focused on unknown primary disease, or they were no longer cited in the revised narrative text. Each study was graded using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence Table. Results: For clinically staged patients undergoing primary (chemo)radiotherapy, we identified 11 new articles published since the initial ACR guideline. Similar to the recommendation in the earlier guideline, unilateral radiotherapy was most often recommended for patients with tumors that were tonsil-confined or either > 1 cm from midline or involving ≤ 1 cm of the mucosa of the base of tongue and/or soft palate. The published experiences demonstrated low rates of contralateral failure in both p16+ and p16- subsets. For patients undergoing primary tumor surgery and being considered for adjuvant radiotherapy, 3 new articles were identified. Multi-disciplinary evaluation is highly recommended before surgery or radiation, since surgical considerations for tonsil cancer may differ from those relevant to ipsilateral RT. The definitions of “well-lateralized” tonsil cancer from a surgical perspective could differ from that of a radiation oncologist. Consequently, whether all surgically resected T1-T2 tonsil SCC with a clinically node-negative contralateral neck are candidates for ipsilateral adjuvant RT warrants further discussion. Collectively among all of the literature reviewed, 1,031 patients were selected for either primary or adjuvant ipsilateral radiotherapy; 26 of 1,031 cases experienced contralateral disease progression. Of these, 19 were reported to have successful salvage and disease control at time of publication. Less than 1% (7 of 1,031) of patients managed unilaterally experienced contralateral progression that was not successfully salvaged. Other factors that might impact the selection for unilateral therapy but remain controversial include: patient age, performance status, number and size of ipsilateral nodes, number of involved ipsilateral nodal stations, clinical/pathological extranodal extension, and p16 status. Conclusions: This updated literature search provided additional information relevant to selection of patients for ipsilateral tonsil radiotherapy in the primary and adjuvant setting. Areas of controversies identified will require further reconciliation and investigation. Updated voting and committee recommendations will be presented.

Radiation Oncology

Wen N, Dai Z, Carver E, Liang E, Snyder J, Griffith B, and Movsas B. Glioblastoma MR Images Synthesis with Generative Adversarial Network. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E28.

Background: Automatic delineation of Glioblastoma (GBM) plays an important role in radiation therapy. Recently, segmentation algorithms using supervised deep neural networks (DNN) have shown promising results, but small volumes of annotated data pose challenges on powering them. Current collection of dataset relies on radiologists' contour as ground truth and is expensive and time-consuming. Objectives: One possible solution to overcome the limitation of small dataset is to generate synthetic MR images representing different clinical scenario. The aim of this study is to apply a generative adversarial network (GAN) to synthesize highly realistic MR images from manipulated annotations that are able to feed as new training samples for DNNs. Methods: Data was obtained from the BraTS multimodal Brain Tumor Segmentation Challenge 2018. 19 different institutions provided a total of 210 patients. T1WI, T1CE, T2WI, and FLAIR were provided for each patient. 82 patients were used for training and 128 patients for validation. The network consisted of a generator and two discriminators. Image per-pixel loss, perceptual loss and adversarial loss were used. By manipulating on annotations from radiologists, the generator was able to output new synthetic MR images, and boost the size of dataset. The realism of synthetic images was evaluated both quantitatively and qualitatively. Results: Synthetic image generated from non-manipulated annotation was compared with its corresponding real image. Mean Square Error (MSE), Mean Absolute Error (MAE), Peak Signal to Noise Ratio (PSNR), and Structural Similarity Index (SSIM) for synthetic MR images were 19.246 ± 0.308 , 23.375 ± 0.586 , 43.068 ± 0.443 and 0.788 ± 0.002 ; 19.249 ± 0.274 , 22.805 ± 0.583 , 43.054 ± 0.437 and 0.789 ± 0.004 ; 19.246 ± 0.290 , 23.391 ± 0.400 , 43.102 ± 0.45 and 0.784 ± 0.003 ; 18.930 ± 0.40 , 24.119 ± 1.48 , 43.126 ± 0.46 and 0.794 ± 0.005 , respectively, for T1, T1CE, T2 and Flair. A subset of 9 real and 10 generated patients were assessed by a physician. 8.3%, 41.7%, 50% of real images and 22.5%, 47.5%, 30% of synthetic images were commented as poor, marginal and good quality. The misclassified rate were 26.3%, 10.5%, 26.3% and 26.3% for T1, T1CE, T2 and Flair. Conclusions: We proposed to apply GAN to synthesize GBM MR images from manipulated annotations to increase the dataset size to train deep learning segmentation models. The evaluation results showed synthetic MRIs had comparable image quality to real MRIs that had potential to be used for DNN training.

Radiation Oncology

Wen N, Sun Z, Zong W, Gardner S, Miller B, Movsas B, and Chetty I. An AI-based Issue Analyzing Framework for Clinical QA Workflow. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E60.

Background: Clinical incident reporting, tracking, and risk analysis are critical parts in the quality assurance (QA) workflow. Traditional incident reporting and learning systems rely heavily on the user input to identify, report, investigate, categorize, and respond to incidents. Text information used in clinical reports has unique terminology and requires special domain knowledge to be processed correctly. Objectives: To develop a workflow utilizing recurrent neural networks (RNN) and a word-to-vector, natural-language processing-(NLP)-based model with oncology domain knowledge, to automatically determine categories and severity level of incidents and identify risks in the clinical workflow. Methods: A total of 3210 existing incident tickets from 16 categories entered by clinical staff over 7 years were used for development of the classification model. Ninety percent of the events were used for training and 10% for validation of the RNN-based algorithm. A subset of 355 tickets with severity level using a 0-10 scale were labeled by physicists for severity estimator model training and validation. Text from the training tickets were preprocessed with lower-casing, punctuation removal, and tokenization, and were fed into an embedding layer. In order to apply oncology domain knowledge to the embedding layer, we trained a word-to-vector model on a total of 286 million words from biomedical research articles obtained from OpenI with keyword "Oncology." Outputs of the forward and backward RNNs were then fed into a softmax output layer for multi-label classification and a linear output layer for regression analysis of the severity level. The AI model were deployed as REST API services which served as an engine to analyze incidents entered through a web application. Immediate feedback was provided through a web interface. Results: After 20 epochs of training, the RNN model reached accuracy of 89.5%, 85.0%, 75.2% for classification of

the top three, two and one categories, respectively. root-mean-square of the severity level prediction reached 0.79 after 74 epochs. A 100-dimensional word-to-vector model was trained using corpus from biomedical articles. T-distributed stochastic neighbor embedding (t-SNE) shows that using word-to-vector model trained from biomedical articles, clinical terms are projected to closer locations in the vector space. Conclusions: A RNN-based incident learning framework for automatic multi-label classification and severity level estimation has been developed. The trained word-to-vector model addressed the word-level label space ambiguity by identifying highly polysemous words that are unique in oncology diagnosis and treatment terminology. Performance of NLP tasks will provide more accurate prediction by using the model trained on quantity incorporating clinical context. Accuracy of the AI-based algorithm is likely to improve with a larger number of events, and more refined categorization of events used for training.

Radiation Oncology

Zong W, Lee J, **Pantelic M**, and **Wen N**. Prediction of Gleason Grade Group of Prostate Cancer on Multiparametric MRI using Deep Machine Learning Models. *International Journal of Radiation Oncology Biology Physics* 2020; 108(2):E9-E10.

Background: The Gleason Grade (GG) Group system has been introduced recently for more accurate stratification of prostate cancer (PCa). The grading system is based on the histologic patterns which is accessed from needle core biopsy, therefore it could be negatively impacted by the intratumor heterogeneity. Objectives: We aim to develop a deep learning algorithm to predict GG groups using multiparametric magnetic resonance images (mp-MRI). Methods: We studied a retrospective collection of 201 patients with 320 lesions from the SPIE-AAPM-NCI PROSTATEx Challenge (<https://doi.org/10.7937/K9TCIA.2017.MURS5CL>), among which 98 patients with 110 lesions with GG available from biopsy. And the number of lesions in each subgroup was 36, 39, 20, 8, and 7, respectively, for GG 1-5. The images were acquired on two different types of Siemens 3T MR scanners. T2W images were acquired using a turbo spin echo sequence and had a resolution of around 0.5 mm in plane and a slice thickness of 3.6 mm. The DWI series were acquired with a single-shot echo planar imaging sequence with a resolution of 2 mm in-plane and 3.6 mm slice thickness and with diffusion-encoding gradients in three directions. Three b-values were acquired (50, 400, and 800 s/mm²), and subsequently, the ADC map was calculated by the scanner software. Image pre-processing included registration and normalization. Image rotation and scaling were also used to increase the sample size and re-balance the number of lesions in various GG. To prevent over-fitting on a small sample size, we implemented a transfer learning model by carrying over the features learned from the malignancy classification of 320 lesions from our previous model into the GG prediction. And we replaced the end-to-end convolutional neural network (CNN) training model with a combination of feature extraction using CNN and classification using weighted extreme learning machine (wELM). Results: Features from the best performing model were extracted to represent each lesion, and those from the last convolutional layer were found constantly better than from all other layers. Based on 3-fold cross validation, the average validation results for sensitivity, specificity, positive predictive value, and negative predictive value for differentiation of each GG (1-5) were (1, 0.99, 0.97, 1), (0.69, 0.85, 0.73, 0.83), (0.9, 0.69, 0.46, 0.97), (0.89, 0.64, 0.16, 0.99), and (1, 0.78, 0.39, 1), respectively. GG4 had the highest false positive values. GG 3 was often misclassified as GG 4. Results of GG3-5 vs. GG1-2 were (0.82, 0.87, 0.76, 0.92). The stratification of GG4-5 vs. GG1-3 was (0.87, 0.81, 0.42, 0.98). Conclusions: This work has made substantial progress tackling the challenging task of GG prediction from mp-MRI due to a smaller and unbalanced data size by transferring knowledge from a malignancy classification task we developed earlier. The combined feature extraction using deep learning model and weighted extreme learning machine classifier has shown promising results for the GG prediction. This work was supported by a Research Scholar Grant, RSG-15-137-01-CCE from the American Cancer Society.

Surgery

Ijaz N, Taleb I, Kyriakopoulos CP, **Demetris Z**, **Peruri A**, Richins TJ, Dranow L, Tang D, **Nemeh H**, Stehlik J, Koliopoulou AG, Selzman CH, Alharethi R, **Cowger J**, Shah P, and Drakos SG. A Novel Risk Score Predicts Early Right Ventricular Failure after Lvad: A Derivation-validation Multicenter Study. *Journal of Cardiac Failure* 2020; 26(10):S149.

Introduction: Right ventricular failure (RVF) after LVAD implantation is associated with increased morbidity and mortality. Despite several RVF predictive models, poor performance in external validation cohorts has limited their widespread clinical adoption. Objective: To develop a novel RVF predictive model, ascertain its performance in an independent validation cohort, and develop an RVF risk score. Methods: Consecutive LVAD patients were prospectively enrolled at the Utah Transplantation Affiliated Hospitals (U.T.A.H) Cardiac Transplant Program (n=477, Derivation cohort). LVAD patients from Inova Heart & Vascular Institute and Henry Ford Medical Center formed the external dataset (n=321, Validation cohort). The primary outcome was early RVF, defined as the need for RVAD or intravenous inotropes for >14 days. The secondary outcome was 3-year all-cause mortality. Multivariable logistic regression analysis was used to develop a predictive model. An RVF risk score was developed using weighted points based on the β -regression coefficients of the multivariable predictors. Results: The study included 798 patients, with a mean age of 56y, 84% male, and 30% INTERMACS Profile 1-2. Compared to the derivation cohort, the validation cohort had a higher proportion of African-Americans (37% vs 7%; p<0.01), patients with a history of HTN (60% vs 49%; p=0.002), and bridging to durable LVAD with short-term MCS (16% vs 8%; p<0.01). The incidence of RVF in the derivation and validation cohorts was 16% and 36%, respectively. Multivariable analysis yielded 7 factors associated with RVF (African-American, history of HTN, INTERMACS profile 1-2, Na <130mEq/L, BUN >35mg/dL, PA pulse pressure <36 mmHg and RA/PCWP >0.5). The model had a c-statistic of 0.73 ([95% CI:0.67-0.79]; p<0.01) and 0.71 ([95% CI: 0.65 - 0.77]; p<0.01) in the derivation and validation cohorts, respectively. A 10-point RVF risk score was developed (Table). The presence of RVF was associated with a higher 1-year (33% vs 12%; p<0.01) and 3-year (39% vs 19%; p<0.01) mortality. Conclusion: We propose a novel scoring system to predict post-LVAD RVF, achieving high discriminative performance after being tested in distinct and highly heterogeneous populations. This simple predictive tool could impact patient selection and perioperative management of LVAD patients.

Surgery

Kalu R, Tang A, and Stefanou A. Pre-Hospital Admission Adversely Affects Outcomes after Colorectal Cancer Surgery: An Analysis of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Database. *Journal of the American College of Surgeons* 2020; 231(4):e107.

Introduction: Colorectal cancer is the third most common cancer in the US. Multiple factors such as age, sex, stage at diagnosis, tumor biology, invasiveness, and setting of surgery, have been shown to affect colon cancer outcomes even with optimal management. Patients usually undergo elective or emergent surgeries for colon malignancy while a significant proportion are admitted to the hospital beforehand. To our knowledge the effect of pre-hospital admission before colorectal surgery has not been previously reported. Using the National Surgical Quality Improvement Program (NSQIP) targeted colectomy database, we evaluated post-surgical outcomes of this patient population. Methods: The NSQIP database (2012-2017) was used to identify patients who underwent colon cancer resections and their preoperative admission status. Multivariate logistic regression weighted by inverse propensity score was performed to compare outcomes of the 2 groups. Results: A total of 9486 patients were evaluated, 50.1% males and 76% Caucasian. Preadmitted patients (12.9%) were significantly older, had multiple comorbidities, and more frequently had open operations. The preadmitted patients had a significantly longer total length of stay (15.9 vs 7.4 days), perioperative bleeding (20.3% vs 12.1%), and wound dehiscence (2.0% vs 1.1%). However, they had lower readmission rates (11.5% vs 14.3%, p<0.05). There was no significant group difference in terms of rates of surgical site infection or reoperation. Conclusion: Compared to their counterparts preadmitted colorectal patients have a significantly longer LOS, bleeding complication, wound dehiscence, but a lower rate of readmission. Further study is needed to assess for long-term cancer-specific outcomes of these patients.

Surgery

Leonard-Murali S, Burmeister C, Susick L, Baker P, and Nathanson S. Where is It? Breast Cancer Location and Associations with Metastasis and Survival. *Journal of the American College of Surgeons* 2020; 231(4):e88-e89.

Introduction: Associations of primary breast cancer (BC) location on development of regional lymph node metastases (RLNM), distant metastases (DM), and mortality remain unclear. We aimed to characterize

any associations, hypothesizing that upper-outer quadrant tumors would be associated with RLNM, DM, and reduced survival. Methods: Hormone-receptor positive, HER2-neu negative BC patients who underwent surgery (including RLN sampling) at a tertiary-care hospital system from 1995-2017 were prospectively reviewed. BC location was described as lower-inner quadrant (LIQ), lower-outer quadrant (LOQ), upper-inner quadrant (UIQ), upper-outer quadrant (UOQ), or central (C). Demographic and clinicopathologic variables were compared between location groups. Kaplan-Meier curves were constructed to analyze mortality by location. Multivariable logistic regression models were constructed to identify associations with RLNM or DM. Significance was established at $p < 0.05$. Results: 1822 patients met inclusion criteria. Location was most often UOQ, and least often C (C=65, 3.6%; LIQ=217, 11.9%; LOQ=244, 13.4%; UIQ=397, 21.8%; UOQ=899, 49.3%). There was no difference in RLNM between groups (C=15, 23.1%; LIQ=51, 23.5%; LOQ=61, 25.0%; UIQ=65, 16.4%; UOQ=204, 22.7%; $p=0.057$), and no difference in DM between groups (C=3, 4.6%; LIQ=21, 9.8%; LOQ=14, 5.8%; UIQ=24, 6.1%; UOQ=58, 6.5%; $p=0.351$). Kaplan-Meier curves showed no difference in survival between groups. By multivariable analysis, UIQ was associated with RLNM (reference group: UOQ; odds ratio=0.67, 95% confidence interval=0.47-0.94; $p=0.021$), with no other associations between location and RLNM or DM found. Conclusion: There were no consistent differences in RLNM, DM, or survival between BC locations. Location does not appear to be a prognostic factor in hormone-receptor positive, HER2-neu negative BC.

Surgery

Rteil A, Bendix S, Nypaver TJ, Weaver MR, and Kabbani LS. Laser Fenestration of Renal Artery in Fenestrated Endograft Repair of Abdominal Aortic Aneurysm. *Journal of the American College of Surgeons* 2020; 231(4):S346-S347.

Introduction: Fenestrated endografts have expanded the indication for endovascular abdominal aortic repair. We present a case of an abdominal aortic aneurysm (AAA) repair with fenestrated endograft (FEVAR) with in situ laser fenestration of the right renal artery. Methods: This is the case of a 72-year-old man who was referred for evaluation of a 5.8 cm abdominal aortic aneurysm (Figure A). Results: Due to the proximity of the right renal artery and superior mesenteric artery (SMA) ostia, a prefabricated fenestrated endograft could not be manufactured. We therefore requested a fenestrated graft with an SMA scallop, a left renal fenestration, and no right renal fenestration. Access to the right renal artery was obtained through the left brachial approach and an uncovered S.M.A.R.T. (Cordis Corporation) was deployed to mark the origin of the right renal artery (Fig. B). A fenestrated endograft (Cook Medical) with a left renal fenestration and an SMA scallop was then deployed (Fig. C). Using the S.M.A.R.T. stent as a target, a fenestration was created using an endovascular laser (Philips Medical) (Fig. D). An iCAST covered stent (Atrium Medical) was then deployed through the new fenestration, and fully expanded using a high-pressure balloon (Fig. E). Another iCAST stent was deployed into the left renal artery. Completion angiogram illustrated patent renal arteries without endoleaks (Fig. F). Postoperative course was uncomplicated, and the patient was discharged on postoperative day 2. [Formula presented] Conclusion: Some aortic pathologies still pose unique challenges to advanced endovascular modalities. FEVAR with in-situ laser fenestration is a feasible option for patients with unfavorable anatomy.

Surgery

Rteil A, Weaver MR, Shepard AD, Nypaver TJ, Lee A, and Kabbani LS. Long-Term Postoperative Outcomes after Abdominal Aortic Aneurysm Repair. *Journal of the American College of Surgeons* 2020; 231(4):e264-e265.

Introduction: Open surgical repair remains the standard of care for Juxtarenal, suprarenal, and Type-IV Thoracoabdominal aortic aneurysms (TAAA). In this study, we reviewed our experience with open surgical Abdominal Aortic Aneurysm (AAA) repair and long-term patient outcomes. Methods: We conducted a retrospective chart review on all patients who underwent open abdominal aortic aneurysm repair between the years 1986 and 2017 at our tertiary care center. Aneurysms were classified as Infraarenal (IR), Suprarenal (SR), Juxtarenal (JR), and Type-IV TAAA. Demographics, co-morbidities, preoperative/postoperative lab values, and patient outcomes were collected. Surgical variables such as operative time, estimated blood loss (EBL), and transfusion requirements were recorded. Multiple comparisons were performed using pairwise chi-square tests or Fisher's exact tests, adjusted with a Bonferroni p-value correction. Results: There were 165 JR-AAA, 81 SR-AAA, 55 Type-IV TAAA, and 318

IR-AAA open repairs on record between 1986 and 2017. Hypertension and COPD were significantly less prevalent in the Infraarenal group ($P=0.0013$ and 0.0017). Intraoperatively, Type IV TAAA repair was associated with a significantly higher EBL ($P<0.001$) and blood transfusion requirements). Postoperatively, Type-IV TAA was also associated with significantly higher pulmonary complications ($P<0.001$). Infraarenal AAA repair was associated with the lowest incidence of postoperative myocardial infarction ($P=0.0493$). There was no significant survival difference among different aneurysm subgroups ($P=0.24$). Conclusion: In our cohort, supraarenal AAA had a higher incidence of hypertension and COPD. As expected, Type-IV TAAA repair was associated with a higher rate of perioperative complications. Long-term survival does not appear to be different among aneurysm subgroups.

Surgery

Varban OA, Bonham AJ, Stricklen A, Ross R, **Carlin AM**, Finks JF, and Ghaferi AA. Am I on Track? Evaluating Patient-Specific Weight Loss after Bariatric Surgery Using an Outcomes Calculator. *Journal of the American College of Surgeons* 2020; 231(4):e1.

Introduction: Individual weight loss outcomes after bariatric surgery can vary considerably. As a result, identifying and assisting patients who are not on track to reach their weight loss goals can be challenging. Methods: Using a bariatric surgery outcomes calculator formulated by the Michigan Bariatric Surgery Collaborative (MBSC), 1-year predicted weight loss was calculated for patients who underwent primary sleeve gastrectomy and gastric bypass between 2015 and 2018 and also had a minimum of 3 follow-up weights reported ($n = 658$). Observed to expected (O:E) ratios were calculated for all patients and weight loss trajectories were compared between patients who met or exceeded their predicted weight loss calculation ($O:E \geq 1$) to those who did not ($O:E < 1$). Results: Patients who did not meet their 1-year predicted weight loss ($n = 237$, mean $O:E = 0.71$) had a lower mean preoperative BMI (46.7 kg/m^2 vs 48.5 kg/m^2 , $p = 0.0079$), were more likely to be black (13.9% vs 8.2% , $p = 0.023$) and had higher rate of hypertension (59.1% vs 48.9% , $p = 0.0124$) when compared with patients who either met or exceeded their weight loss prediction ($n = 421$, mean $O:E = 1.14$). Patients who did not meet their weight loss prediction also had less mean total body weight loss (19.8% vs 29.6% , $p < 0.0001$) and were noted to have a lower O:E ratio as early as 3 months after surgery (0.50 vs 0.58 , $p < 0.0001$). Conclusion: Using a bariatric-specific weight-loss calculator, individuals can determine if they are on track to meeting their predicted weight loss calculation as early as three months after surgery.

Books and Book Chapters

Surgery

Ahmed S, and Sharman T. "Intestinal Pseudo-Obstruction". *StatPearls*. Treasure Island (FL), StatPearls Publishing. 2020. [Full Text](#)

Intestinal pseudo-obstruction is characterized by the dilation of bowel in the absence of an anatomical obstruction. Patients present with the signs and symptoms of bowel obstruction, including nausea, vomiting, abdominal distension, and obstipation with bowel dilation on x-ray or CT imaging. Pseudo-obstruction can be acute or chronic. Acute colonic pseudo-obstruction (ACPO), also known as Ogilvie syndrome, most commonly affects the large intestine from the cecum to the splenic flexure. The exact pathophysiology is unknown, but it has been linked to dysregulation of the autonomic nervous system. Most cases are found in patients who have undergone surgery or are critically ill. After a mechanical obstruction is ruled out, initial management includes bowel rest, nasogastric decompression, intravenous fluid resuscitation, and treatment of the underlying cause. Further treatment options include administration of Neostigmine as well as endoscopic, percutaneous, or surgical decompression. Chronic intestinal pseudo-obstruction (CIPO) is a more rare form of pseudo-obstruction, usually causing early satiety, nausea, bloating, and distension. Causes are usually infectious, metabolic, neurologic, autoimmune, or idiopathic.

Surgery

Stauffer CM, Meshida K, Bernor RL, Granite GE, and Boaz NT. "Anatomy, Thorax, Pericardiophrenic Vessels". *StatPearls*. Treasure Island (FL), StatPearls Publishing. 2020. [Full Text](#)

The pericardiophrenic artery and vein make up, with the phrenic nerve, the pericardiophrenic neurovascular bundle. The vessels pass through superior thoracic aperture into the superior mediastinum and course along the pathway of the phrenic nerve anterior to the lung roots. The vessels are located between the fibrous pericardium and the parietal pleura in the middle mediastinum and extend inferiorly onto the dome of the diaphragm. The pericardiophrenic artery supplies blood to the pericardium, diaphragm, and phrenic nerve. While the pericardiophrenic arteries supply blood to these various tissues, and they are a non-coronary arterial collateral blood supply to the heart. Their most important role clinically is to supply the phrenic nerve with blood when harvesting or surgically anastomosing the internal thoracic artery, as in CABG procedures, preserving blood flow in the pericardiophrenic artery is important to prevent any ischemic damage to the phrenic nerve. The pericardiophrenic veins are variable tributaries of the right and left brachiocephalic veins (also formerly known as the innominate veins) or internal thoracic veins. The pericardiophrenic veins are a minor portocaval anastomosis connecting splenic vein and superior vena cava and can become engaged in portal hypertension. Imaging the pericardiophrenic veins (or arteries) is a reliable aid in clinical procedures that require locating the phrenic nerve.

HFHS Publications on COVID-19

Behavioral Health Services/Psychiatry

Imtiaz Memon R, Imran N, Aamer I, Imran Sharif M, Hassan Bodla Z, and Naveed S. 1.16 THE EFFECT OF QUARANTINE ON THE EMOTIONAL WELL-BEING OF KIDS: A SYSTEMATIC REVIEW. *Journal of the American Academy of Child and Adolescent Psychiatry* 2020; 59(10):S144. Conference Abstract.

Cardiology and Cardiovascular Research

Fram G, Wang DD, Malette K, Villablanca P, Kang G, So K, Basir MB, Khan A, McKinnon JE, Zervos M, and O'Neill WW. Cardiac Complications Attributed to Hydroxychloroquine: A systematic review of the Literature Pre-COVID-19. *Curr Cardiol Rev* 2020; Epub ahead of print. PMID: 33059567. [Request Article](#)

Cardiology/Cardiovascular Research

Raad M, Gorgis S, Dabbagh M, Parikh S, and Cowger J. Characteristics and Outcomes of Patients with Heart Failure Admitted with Covid-19 in a Cohort Study from Southeast Michigan. *Journal of Cardiac Failure* 2020; 26(10):S74. Conference Abstract.

Diagnostic Radiology

Boregowda U, Gandhi D, Jain N, **Khanna K**, and Gupta N. Comprehensive Literature Review and Evidence evaluation of Experimental Treatment in COVID 19 Contagion. *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine* 2020; 14. PMID: Not assigned. [Full Text](#)

Diagnostic Radiology

Poyiadji N, Klochko C, LaForce J, Brown ML, and Griffith B. COVID-19 and Radiology Resident Imaging Volumes-Differential Impact by Resident Training Year and Imaging Modality. *Acad Radiol* 2020; Epub ahead of print. PMID: 33046369. [Full Text](#)

Infectious Diseases

Fram G, Wang DD, Malette K, Villablanca P, Kang G, So K, Basir MB, Khan A, McKinnon JE, Zervos M, and O'Neill WW. Cardiac Complications Attributed to Hydroxychloroquine: A systematic review of the Literature Pre-COVID-19. *Curr Cardiol Rev* 2020; Epub ahead of print. PMID: 33059567. [Request Article](#)

Infectious Diseases

Shallal A, Kenney R, and Weinmann A. Missed Vaccine Opportunities to S. pneumoniae and Influenza in Patients Admitted During the COVID-19 Pandemic. *Infect Control Hosp Epidemiol* 2020; Epub ahead of print. PMID: 33100230. [Full Text](#)

Nephrology

Shrivastava P, Prashar R, Khoury N, Patel A, Yeddula S, Kitajima T, Nagai S, and Samaniego M. Acute Kidney Injury in a Predominantly African American Cohort of Kidney Transplant Recipients With COVID-19 Infection. *Transplantation* 2020; Epub ahead of print. PMID: 33093403. [Full Text](#)

Pharmacy

Shallal A, Kenney R, and Weinmann A. Missed Vaccine Opportunities to S. pneumoniae and Influenza in Patients Admitted During the COVID-19 Pandemic. *Infect Control Hosp Epidemiol* 2020; Epub ahead of print. PMID: 33100230. [Full Text](#)

Public Health Sciences

Corley DA, Sedki M, Ritzwoller DP, Greenlee RT, **Neslund-Dudas C**, Rendle KA, Honda SA, Schottinger JE, Udaltsova N, Vachani A, Kobrin S, Li CI, and Haas JS. Cancer Screening during COVID-19: A Perspective from NCI's PROSPR consortium. *Gastroenterology* 2020; Epub ahead of print. PMID: 33096099. [Full Text](#)

Pulmonary and Critical Care Medicine

Berry LL, and **Adawi Awdish RL**. Health Care Organizations Should Be as Generous as Their Workers. *Ann Intern Med* 2020; Epub ahead of print. PMID: 33076692. [Full Text](#)

Radiation Oncology

Vscariello I, Evans S, Parker S, Schofield D, **Miller B**, Gardner S, Fong de Los Santos L, Hallemeier C, Jordan L, Kim E, and Ford E. A multi-institutional assessment of COVID-19-related risk in radiation oncology. *Radiother Oncol* 2020; Epub ahead of print. PMID: 33096163. [Full Text](#)

Surgery

Shrivastava P, Prashar R, Khoury N, Patel A, Yeddula S, Kitajima T, Nagai S, and Samaniego M. Acute Kidney Injury in a Predominantly African American Cohort of Kidney Transplant Recipients With COVID-19 Infection. *Transplantation* 2020; Epub ahead of print. PMID: 33093403. [Full Text](#)