YALE SURGERY RESEARCH DAY 2025

KEYNOTE SPEAKER

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Dr. Carol Swallow is the RS McLaughlin Professor and Chair of the Department of Surgery at the University of Toronto. She is a surgical oncologist at Princess Margaret Hospital and a member of the Division of General Surgery at Mount Sinai Hospital in Toronto. She graduated from the University of Toronto Medical School and trained in the General Surgery residency program at the University of Toronto as a member of the Surgical Scientist Training Program, completing a PhD in cell biology and surgical sepsis in 1993. After this, she completed clinical fellowship training in Surgical Oncology at Memorial Sloan Kettering Cancer Center. She is currently a Professor in the Department of Surgery and Institute of Medical Science at the University of Toronto. Her areas of clinical expertise include retroperitoneal sarcoma, gastrointestinal stromal tumour, gastric cancer, and rectal cancer. Her laboratory research is focused on mechanisms of tumour invasion and metastasis. Dr. Swallow was the Director of the University of Toronto General Surgical Oncology Fellowship Program from 1997-2009, Head of the Division of General Surgery at Mount Sinai Hospital from 2008 to 2019, Chair of the Division of General Surgery at the University of Toronto from 2014 - 2022, and Chair of the Department of Surgery at U of T since July 1, 2022. She is currently the Past-President of the Connective Tissue Oncology Society and a Section Editor for the Annals of Surgical Oncology. She is the author of over 170 peer-reviewed papers.

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ABSTRACTS

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BASIC SCIENCE ABSTRACTS

PHOSPHODIESTERASE 10A REGULATES MEDIAL ARTERIAL CALCIFICATION THROUGH P38/MAPK-MMP3 SIGNALING

Jin Y, Xie Y, Berezowitz AG, Davis S, Flores AM, Wang X, GuzmanRJ, Cai Y

Introduction: Vascular calcification is a significant factor contributing to the high incidence and elevated mortality rate of cardiovascular diseases. Patients with chronic kidney disease (CKD), diabetes, and peripheral artery disease (PAD) are particularly prone to vascular calcification. Phosphodiesterase (PDE) 10A is a key regulator of the cyclic nucleotides cAMP and cGMP, andpivotalin a variety of cardiovascular events. However, the role of PDE10A involved in the medial artery calcification remains unclear.

Methods: High phosphate media were used to induce calcification in vascular smooth muscle cells (VSMCs). Besides, qRT-PCR, immunohistology staining and immunofluorescent staining were applied to evaluate the PDE10A expression level. Von kossa staining and calcium assay were performed to assess the calcification level. Moreover, two types of in vivo rodent calcification models, vitamin D3 injection and 5/6 nephrectomy, were established to evaluate medial calcification.

Results: PDE10A was the most highly induced isoform in the rodent model of arterial calcification. The expression level of PDE10A was increased in calcifying VSMCs in vitro, calcified arteries from rodents with CKD, and calcified human tibial arteries. PDE10A knockdown or inhibition significantly attenuated VSMC osteogenic transformation and calcification in vivo and in vitro. Furthermore, PDE10A deficiency significantly decreased arterial calcification in ex vivo aortic ring, in vivo vitamin D3 medial calcification models and in vivo 5/6 nephrectomy-induced calcification models. In addition, PDE10A regulated matrix metallopeptidases-3 (MMP-3) expression in calcifying VSMCs and could regulate vascular calcification by controllingp38 MAPK signaling and MMP-3 activity through cGMP/PKG signaling.

Conclusion: PDE10A is critical in the development of medial artery calcification through biased activated p38 MAPK-MMP3 signaling. Our findings suggest that targeting PDE10A should offer therapeutic benefits for patients with PAD and CKD to reduce calcification, and ultimately decrease major limb amputation risks.

SMOOTH MUSCLE CELL-SPECIFIC MMP-3 DELETION REDUCES OSTEOGENIC TRANSFORMATION AND MEDIAL ARTERY CALCIFICATION

Xie Y, Lin T, Berezowitzi AG, Wang X, Lu J, Cai Y, Guzman RJ

Introduction: Vascular calcification is highly prevalent in atherosclerosis, diabetes, and chronic kidney disease. It is associated with increased morbidity and mortality in patients with cardiovascular disease. Matrix metalloproteinase 3 (MMP-3), also known as stromelysin-1, is part of the large matrix metalloproteinase family. It can degrade extracellular matrix components of the arterial wall including elastin, which plays a central role in medial calcification. In this study, we sought to determine the role of MMP-3 in medial calcification.

Methods: Using calcium assay, siRNA knockdown, and transgenic mice.

Results: We found that MMP-3 expression was increased in vascular smooth muscle cells (SMCs) cultured in a phosphate calcification medium. It was also highly expressed in calcified tibial arteries from patients with peripheral arterial disease (PAD). Knockdown and inhibition of MMP-3 suppressed phosphate-induced SMC osteogenic transformation and calcification, whereas the addition of a recombinant MMP-3 protein facilitated SMC calcification. In an ex vivo organ culture model and a rodent model of medial calcification induced by vitamin D3, we found that MMP-3 deficiency significantly suppressed aortic medial calcification, suggesting that MMP-3 in SMCs is crucial for medial calcification.

Conclusion: These findings suggest that MMP-3 expression in vascular SMCs is an important regulator of medial calcification and that targeting MMP-3 could provide a therapeutic strategy to reduce it and address its consequences in patients with PAD.

A NOVEL MODEL FOR DEGENERATIVE MITRAL VALVE DISEASE

Ghodsi A., Sotolongo A.*, Kuebler S.*, Luna E., Gao F., Krane M., and Gruber PJ. (*equal contributions)*

Introduction: Non-syndromic degenerative mitral valve disease (dMVD) is the most common cause of mitral regurgitation and requires prompt detection and surgical intervention to maintain a normal life expectancy in affected individuals. The morphological phenotype of dMVD ranges from fibroelastic deficiency (FED) to Barlow's disease. The current understanding of the pathophysiologic mechanisms and genetic landscape is inadequate for distinguishing clinically benign and malignant mitral valve abnormalities prior to the development of pathologic regurgitation. Additionally, there is strong evidence for the heritability of dMVD, though few pathogenic loci have been identified to date.

Methods: From a cohort of 2,159 European patients with dMVD requiring surgery at the German Heart Center Munich, 400 individuals (200 with FED and 200 with Barlow's disease) were selected for whole exome sequencing. Variants were filtered based on expression, quality, allele frequency, and pathogenicity. We created a Sipa1L1 null mouse model using a gene trap construct and standard gene targeting techniques. Primary cardiac fibroblasts were used for RNA sequencing analysis to compare differential gene expression between Sipa1L1 knockout and wildtype mice. Further in vitro analysis were performed.

Results: We identified several novel loci in the WES study enriched in Barlow compared to the FED phenotypes. Signal Induced Proliferation Associated 1 (SIPA1L1) Like 1 was enriched in the Barlow's disease phenotype. SIPA1L1 is a member of the RapGAP superfamily associated with the organization of the actin cytoskeleton and modulation of GTPase activity. We created Sipa1l1 deficient mice. Despite being viable and fertile, Sipa1L1 null mice demonstrate a Barlow's disease-like phenotype with thickened mitral leaflets. Primary cardiac fibroblasts were used for RNA sequencing analysis to compare differential gene expression between Sipa1L1Null vs Sipa1L1WTmice. Further, in vitro analysis revealed increased cellular migration, reactive oxygen species, and expression of matrix metalloproteinase 13.

Conclusion: Identification of candidate genes and their unique temporal expression patterns in the developing and mature mammalian mitral valve using genome-wide studies enables the investigation of genetic and molecular mechanisms of dMVD. Furthermore, analysis of phenotype specific variants reveals distinct profiles for FED and Barlow's disease suggests dMVD subtypes are produced by specific transcriptional and regulatory phenomena. Elucidating the molecular pathways and genetic basis of dMVD and its associated phenotypes promises to advance the development of clinical markers and therapeutics.

SLU7 REGULATES CARDIAC DEVELOPMENTAL PROGRAMS AND CONTRIBUTES TO THE PATHOGENESIS OF HYPOPLASTIC LEFT HEART SYNDROME

Yang Y., Luna E.*, Ghodsi A.*, Pickell Z., Han Z., Krane M., Bowles N., Baccam G., Lester H., Hein L., Meitinger T., Laugwitz K., Moretti A., and Gruber PJ. (* contributed equally)*

Introduction: Hypoplastic left heart syndrome (HLHS) is a severe form of congenital heart disease characterized by an underdeveloped left ventricle and is fatal without surgical intervention. No studies have used large-scale sequencing of HLHS patients to identify genomic targets with subsequent target validation in vivo. This study emphasizes the profound genetic diversity of HLHS, emphasizing the need for multiple approaches and patient-specific analyses to understanding the pathogenesis of HLHS.

Methods: Whole exome sequencing was conducted on 87 patients with HLHS. Knockdown of slu7 was performed in Drosophila. SLU7 knockdown was performed in human cardiac cell lines. Cardiac-specific Myh6:Slu7 gene-targeted mice and a humanized SLU7K302R mouse were created.

Results: Knockdown of slu7 in Drosophila resulted in embryonic lethality and was rescued with humanSLU7WT but not with SLU7K302R. SLU7K302R significantly decreased mRNA splicing efficiency compared toSLU7WT. Moreover, SLU7knockdown resulted in defects in transcriptional and alternative splicing of many developmental programs essential for cardiac embryogenesis. One of the aberrantly spliced products is the chromatin-modifying gene KMT2D, the most commonly mutated gene in human HLHS. We examined the effect ofSLU7K302R on RNA splicing efficiency using luciferase splicing reporters. Human cardiac myocytes were transfected with SLU7siRNA and collected for RNA-Seq and analyzed using DESeq2, JunctionSeq, and RMATs. GSEA was performed to analyze expression datasets and annotate the enrichment results. Further investigation used two murine Slu7 knockout models, constitutive and cardiac-specific. Slu7 constitutive nulls were early embryonic lethal; cardiac-specific Myh6:Slu7 homozygotes were present at mid-gestation but not at birth.

Conclusion: These findings expand our knowledge of the genetic landscape of HLHS, emphasizing the need to go beyond in silico analyses to understand the mechanism. Our studies demonstrate slu7/Slu7/SLU7 as a critical factor in RNA processing and cardiac development in flies, mice, and humans. Further investigation is underway to understand the role of SLU7 andSLU7K302R in murine cardiac morphogenesis. These pathways build a knowledge base to enable the development of rational therapeutic and counseling strategies for this set of patients.

THE FIRST LARGE ANIMAL MODEL FOR VASCULARIZED LYMPH NODE ALLOTRANSPLANTATION

Stoian, A., Bach, K., Duru, C., Haykal, S.

Introduction: The lymphatic system (LS) is a network of organs, vessels, and tissues crucial for maintaining fluid balance, lipid absorption, and immune function. When the LS is compromised, it can lead to lymphedema, a chronic and progressive condition characterized by the accumulation of lymphatic fluid, causing tissue swelling, pain, and functional disability. Lymphedema is usually a secondary condition, often caused by oncologic therapy. Treatment for lymphedema has long been considered conservative and limited, but in recent years, more surgical procedures have been developed, with vascularized lymph node transfer (VLNT) emerging as one of the most promising options. Two theories explain how VLNT works: (i) transplanted LNs create a low-pressure area that collects lymph and transfers it into the venous system, and (ii) transplanted lymphatic tissue promotes the development of new drainage channels, and this lymphangiogenesis is believed to be driven by vascular endothelial growth factor-C (VEGF-C). Lymphatic tissue engineering (LTE) is a promising, relatively young field focused on creating functional extracellular scaffolds and lymphatic structures. This work introduces the first large animal model for vascularized LN allotransplantation, employing tissue engineering (TE) methods.

Methods: This study leveraged Yorkshire pigs to establish a large animal model for vascularized LN allotransplantation. The work focused on developing: (i) a protocol for procuring vascularized inguinal LN, (ii) a decellularization protocol based on ex vivo perfusion techniques, a low-concentration detergent solution, and enzyme treatment, and (iii) a preconditioning protocol designed to enhance the VEGF-C concentration in the extracellular matrix (ECM) of the LNs.

Results: We have developed a simple and efficient procurement protocol for vascularized LNs, which can be used in future research studies involving LTE. The decellularization of the LNs was confirmed by the absence of nuclear cells in H&E staining and a significant reduction in DNA content. The preservation of the ECM structure was analyzed through sGAG quantification. Preliminary data are being collected to evaluate the preservation of VEGF-C and the efficiency of the preconditioning protocol.

Conclusion: We have successfully established a reliable protocol for procuring and decellularizing vascularized LNs in a large animal model. Preliminary results suggest that the protocol is effective in maintaining ECM structure and sets the stage for further studies on VEGF-C preservation, VEGF-C augmentation, and future TE applications.

TRANSPLANTATION OF ADIPOCYTE PRECURSOR CELLS TO TREAT DIABETIC NON-HEALING WOUNDS

*Daqian Gao, Avery Lee, Henry C. Hsia**

Introduction: Non-healing wounds are a common source of morbid complication in patients with diabetes. While decellularized extracellular matrix (dECM) products and growth factors are frequently used in clinic, the repair outcomes are usually poor. It remains challenging to develop viable treatments for diabetic wounds, because the cellular and molecular mechanisms that promote healing are not well understood.

Methods: Our preliminary studies identified multiple fibroblast subpopulations in both human and mouse skin. Notably, adipocyte precursor cells (APs), a critical fibroblast subpopulation, lost their adipogenic potential, migrated into wound beds and formed long-lived myofibroblasts during the proliferation phase of wound healing via IGF-1 signaling pathway. The percentage of APs drastically decreased in diabetic and aged mice.

Results: Therefore, our hypothesis is that transplantation of healthy APs can restore cellular interactions and promote diabetic wound healing. In Aim 1 of this study, the role of APs in diabetic wounds will be determined. Our preliminary data also revealed that the expression of thrombospondin-2 (TSP-2), a matricellular protein, increased in diabetic wounds. Deletion of TSP-2 in db/db mice improved wound healing. In Aim 1, it will be also evaluated whether TSP-2 knockout (KO) ECM hydrogel can support and promote the functions of APs. In Aim 2, it will be further determined whether transplantation of APs using TSP-2 KO ECM hydrogel can accelerate and enhance diabetic wound healing.

Conclusion: Undoubtedly, this study will provide a novel cell therapy for efficiently treating diabetic non-healing wounds. This study will also provide important information for cellular and molecular mechanisms underlying diabetic non-healing wounds.

PERINEURAL INVASION IS ASSOCIATED WITH DECREASED T-CELL INFILTRATION IN SALIVARY GLAND CANCERS WITH FACIAL PALSY

Munshi M, Ladenheim AE, Schiff B, Sayed Z, Verma A, Mehra S, Judson B, Roche A, Pai SI, Mohan S

Introduction: Perineural invasion (PNI) is a key mechanism facilitating tumor progression in head and neck cancers (HNCs) and is associated with a poorer prognosis. The presence of PNI in major salivary gland (MSG) cancers is often associated with facial palsy and a higher risk of local recurrence and distant metastasis. This pilot study aimed to characterize the tumor immune microenvironment in MSG cancers with PNI to elucidate whether direct tumor nerve invasion alone or an associated inflammatory response is responsible for facial palsy and associated poorer prognosis.

Methods: MSG cancers with PNI were identified from the Yale Head and Neck Biorepository. Tumor infiltrating lymphocyte (TIL) populations in the tumor and perineural zone were quantitated using H&E and immunohistochemistry (CD3, rabbit polyclonal antibody, Biocare Medical, Pacheco, CA) staining. The perineural zone was defined as the area within one high powered field (HPF, 400x) of a tumor-involved nerve. The overall TIL density was characterized on H&E-stained sections as a ratio of the area occupied by TILs to area occupied by the tumor cells and stroma. The absolute number of TILs per high power field were counted in the areas of highest density (‘hotspots’) in both tumor and in perineural zones. Histologic findings were correlated with clinical signs including facial palsy and survival.

Results: Ten cases with PNI were studied: five primary MSG cancers (adenoid cystic, secretory, and salivary duct carcinomas) and five metastatic squamous cell carcinomas (SCC) to the MSG. Mean patient age was 75 years (range 36-99). Median survival was 1.79 years (range 0.31-8.53). Preoperative facial palsy was present in 60% (6/10) of cases, all of which (100%, 6/6) demonstrated extensive extratumoral PNI. In 90% (9/10) of cases, the CD3+ TIL counts were lower in perineural zones compared to hotspots within the tumor. The mean difference in CD3+ TIL counts was 47.5 cells/HPF (CI: 17.42 to 77.58, p=0.006). Primary MSG cancers as compared to metastatic SCCs had the lowest frequency of TILs in the perineural environment (mean 20/HPF vs 54/HPF, respectively) as compared to the tumor overall (mean 54/HPF vs 120/HPF, respectively).

Conclusion: PNI is associated with a decreased CD3+ TIL population in MSG cancers and metastatic SCCs. Therefore, the associated facial palsy is a result of direct tumor invasion of the nerve rather than a host inflammatory response, as observed in Bell’s palsy. Next steps aim to determine whether PNI induces an immune privileged milieu facilitating tumor growth and invasion.

SPATIAL PROTEOMIC AND TRANSCRIPTOMIC PROFILING OF MELANOMA BRAIN METASTASES EXHIBIT ELEVATED NEURAL CELL ADHESION MOLECULE 1 (NCAM1) EXPRESSION AND ASSOCIATIONS WITH IMMUNE MICROENVIRONMENT AND TREATMENT RESPONSE

Su DG, Gaiger NS, Schoenfeld DA, Djureinovic D, Dong M, McNamara M, Galan A, Olino K, Chiang V, Adeniran A, Jilaveanu L, Kluger HK.

Introduction: Melanoma brain metastases (MBM) affect approximately 60% of patients with metastatic melanoma and exhibit distinct molecular and immune features compared to extracranial metastases (ECM). Prior studies have demonstrated a unique immune microenvironment in MBM, including increased CD8+ T-cell infiltration and pro-tumorigenic macrophages. However, the spatial architecture of the MBM ecosystem remains incompletely understood. In this study, we explore the immunoproteomic landscape and cellular composition of MBM.

Methods: A tissue microarray (TMA) comprising 353 cores of matched tumor and normal adjacent human tissue specimens from MBM or ECM was constructed. High-plex proteomic and transcriptomic analysis was performed using the Nanostring GeoMx and CosMx platforms with spatial resolution. In GeoMx Digital Spatial Profiler (DSP), a 68-plex protein panel was quantified simultaneously in three fluorescence-based tissue compartments [tumor (PMEL+/MART1+/SOX10+), leukocytes (CD45+), and macrophages (CD68+)]. A 6,000-plex RNA CosMx panel was applied for spatial transcriptomic profiling. A second independent cohort of MBM patients was applied for external validation.

Results: Of 52 patients with melanoma brain metastases, 60% were female (31/52) and the median age was 56. 67% (35/52) received immunotherapy (IT), and majority were located on the trunk (35%) or lower extremities (21%). 42% of cases yielded either a complete (CR) or partial (PR) response to IT, 21% had stable disease (SD), and 36% had progressive disease (PD). Patients with higher CD3+, CD4+, and CD8+ expression in the CD45+ compartment in MBM samples exhibited improved overall survival ($p = 0.027$, $p = 0.0053$, $p = 0.016$). NCAM1 protein expression in both CD45+ and tumor compartments was differentially expressed in MBM samples compared with ECM ($p = 0.0359$, $p = 0.003$). IT responders (CR/PR) demonstrated higher NCAM1+ cell prevalence in the CD45+ and tumor compartments compared to non-responders (SD/PD). NCAM1 overexpression in MBM was validated in a secondary cohort, and patients with low NCAM1 expression exhibited prolonged brain metastasis-free survival (BMFS). Spatial transcriptomic mapping revealed NCAM1 localization patterns in tumor-dense regions.

Conclusion: NCAM1 protein expression is elevated in MBM and may be associated with early development of brain metastasis and improved survival, suggesting NCAM1 may be a potential biomarker for MBM progression and therapeutic targeting. Further studies are warranted to elucidate its mechanistic role in tumor-immune interactions and adhesion pathways in the brain microenvironment.

CD45RO-BASED DIGITAL SPATIAL PROTEOMIC SIGNATURES PREDICT IMMUNOTHERAPY RESPONSE IN MELANOMA

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Introduction: Melanoma, an aggressive and immunogenic form of skin cancer, presents significant treatment challenges due to the varied responses patients exhibit to immune checkpoint inhibitors (ICIs). Our work aims to identify predictive biomarkers for ICI response in advanced melanoma by using digital spatial profiling (DSP) of protein expression within the tumor immune microenvironment (TME).

Methods: We investigated spatial protein expression in two independent cohorts of melanoma patients (A: 69; B: 51) treated with PD-1-based monotherapy or dual PD-1/CTLA-4 therapy. Tumors were stained with fluorescent antibodies against S100/PMEL (tumor), CD45 (immune), and SYTO (nuclear dye) to define compartments and captured with an oligo-based 68 plex protein panel for proteomic analysis. For analysis, we employed univariable and multivariable analyses, as well as LASSO Cox regression models to assess response and resistance to therapy.

Results: In the tumor compartment, CD45RO expression was significantly associated with better progression-free survival (PFS), with an HR of 0.37 (95% CI: 0.198–0.699) and an adjusted p-value of 0.014. In the CD45+ immune cell compartment, CD45RO, CD95/Fas, and Ki67 emerged as predictive features of treatment resistance in the training cohort (HR = 1.8, 95% CI: 1-3.4, p = 0.05). However, this signature did not achieve validate in the independent cohort (HR = 1.4, 95% CI: 0.77-2.5, p = 0.13). In the CD68+ macrophage compartment, CD45RO, CD44, and Ki67 were identified as predictive features of treatment resistance in the training cohort (HR = 1.9, 95% CI: 1-3.5, p = 0.04). This signature was successfully validated in the validation cohort (HR = 1.8, 95% CI: 0.96-3.2, p = 0.03).

Conclusion: Our proteomic analysis revealed CD45RO as a potential marker for treatment resistance. The identification of compartment-based biomarkers has implications for providing predictive power in the response to immunotherapy.

USE OF NICOTINIC ACID TO WIDEN THE THERAPEUTIC INDEX OF NAMPT INHIBITOR FK866 IN NEUROBLASTOMA

Rehman S., Lucas K., Kim A., Hellmann Z., Friedman S., Cowles RA., Stitelman D., Christison-Lagay E., Vasquez JC.

Introduction: High-risk and recurrent neuroblastoma continue to carry poor prognoses; thus, new therapeutic strategies are needed. One emerging strategy exploits the Warburg Effect, an observation that rapidly dividing neoplastic cells preferentially generate ATP via glycolysis and thus, require increased turnover of nicotinamide adenine dinucleotide (NAD+). NAD+ is generated via one of three pathways: de novo synthesis, Preiss-Handler and nicotinamide (NAM) salvage. The rate limiting enzymes for the Preiss-Handler and NAM salvage pathways are nicotinate phosphoribosyltransferase (NAPRT) and nicotinamide phosphoribosyltransferase (NAMPT) respectively. The clinical translation of NAMPT inhibitors has been limited by dose limiting toxicities, particularly thrombocytopenia. NAPRT is essential for cells to convert nicotinic acid to NAD+ and a subset of tumors are known to lack this protein. We hypothesize that treatment of neuroblastoma with NAMPT inhibitor, FK866, plus nicotinic acid would result in a differential response based on NAPRT status due to rescue of NAD+ levels via the Preiss-Handler pathway.

Methods: The Cancer Dependency Map Project at Broad Institute was queried for NAPRT methylation and protein expression across tumor types. We confirmed NAPRT status in four human cell lines: SKNAS, CHP 212, SKNDZ, and SKNBE2. We performed a growth development assay by treating each cell line with serial dilutions of FK866 +/- nicotinic acid supplementation. We used the Promega NAD+ assay kit to confirm NAD+ depletion in response to FK866 treatment.

Results: NAPRT is both methylated at a higher rate and expressed at a lower rate in neuroblastoma compared to other tumor types. We confirmed SKNAS and SKNBE2 are NAPRT positive while CHP 212 and SKNDZ are NAPRT negative. Treatment with FK866 is effective in neuroblastoma and NAD+ levels in cells with intact NAPRT can be rescued with nicotinic acid. NAMPT inhibition with FK866 +/- nicotinic acid showed NAD depletion in response to NAMPT inhibition that was rescued with NA only when NAPRT is present.

Conclusion: NAPRT is highly methylated and protein abundance is lower in neuroblastoma relative to other tumor types. NAPRT negative status confers a synthetic lethality to NAMPT inhibition plus nicotinic acid supplementation, which can be leveraged to achieve anti-tumor effect via depletion of NAD+ at the tumor level while rescuing NAD+ levels in normal cells to potentially mitigate dose limiting toxicity.

ACUTE REJECTION IS ASSOCIATED WITH SIGNATURE DONOR-DERIVED CELL FREE DNA PROFILE FOLLOWING FACE TRANSPLANTATION IN A RODENT

Olivier F. Noel, Luis Gonzales, Yiting Xu, Kristyn Carter, Lioba Huelsboemer, Viola Stogner, Mica Williams, Valerie Horsley, Bohdan Pomahac

Introduction: Face transplantation (FT) has revolutionized the way we treat patients with severe disfiguration resulting from trauma, such as burns, motor vehicle accidents, gunshot wounds, and massive tumor resection. However, acute rejection remains a significant challenge after face transplantation, which can lead to allograft loss. Noninvasive biomarkers such as donor derived cell-free DNA (ddcfDNA) have shown great promise in solid organ transplantation rejection monitoring and several studies and clinical trials have demonstrated its clinical utility. However, within the field of vascularized composite allotransplantation very little is published on the potential of ddcfDNA for graft monitoring, as studies lack on characterizing the differential expression and genetic profile of ddcfDNA following face transplantation.

Methods: The authors performed face transplant on rodents using several inbred donors (Fischer, Long-Evans, Sprague Dawley) and Lewis recipient rats. Microsurgical anastomosis of the common carotid artery and external jugular vein were performed. Animals were not given immunosuppression postoperatively and allowed to undergo acute rejection. The authors analyzed plasma and tissue at time of rejection (confirmed with histology and immunofluorescence) with subsequent cfDNA extraction and Next-Generation Sequencing. ddcfDNA was quantified and characterized on the basis of Small Nucleotide Polymorphism (SNPs) and correlated with acute rejection.

Results: Acute rejection was achieved within an average of 5.3±2 days following hemiface transplantation as allografts demonstrated skin necrosis. The authors identified SNPs that match the face transplant donor animal's DNA and not the recipient's DNA, establishing these regions as ddcfDNA. The authors found that on average, clinical rejection was observed when the face transplanted animal's cfDNA contains 0.31% or more of the donor cfDNA. Furthermore, the authors identified a total of 313 SNPs – mapping to 49 genes – unique to the donor genome which were consistently detected in face transplanted animals across breeds.

Conclusion: These findings characterize a signature ddcfDNA profile associated with acute rejection after face transplantation in a rodent model. These findings are of paramount interest as potential rejection markers and may prove to be the basis for the clinical use of ddcfDNA for acute rejection monitoring.

MACRO-PATCH VOLTAGE CLAMP EVALUATION OF SUB-MEMBRANOUS CHLORIDE LEVELS IN THE OHC LATERAL MEMBRANE.

Santos-Sacchi, J., Tan, W. and Navaratnam, D.

Introduction: Prestin is responsible for cochlear amplification which supports high frequency hearing. A fundamental property of prestin is its sensitivity to intracellular chloride. Boltzmann fits (2-state-Csa; Santos-Sacchi and Navarrette, Pflugers Arch, 2002) determine Qmax, Vh, z and delta-Csa, the latter thought to correspond to changes in membrane surface area/thickness that occur in sync with prestin conformational change across voltage. Here we explore the influence of chloride binding on prestin characteristics with the macro-patch technique, and compare to whole cell measures.

Methods: In guinea pig membrane patches, first on-cell then excised, we measured prestin's Boltzmann parameters during changes under voltage clamp using AC measures of NLC (nonlinear capacitance) at 1 kHz. By comparing on-cell patch characteristics to subsequent excised inside-out patch characteristics perfused with 1, 10 and 150 mM chloride, we are able to estimate chloride levels in the intact OHC.

Results: Our data indicates that on-cell Vh is closest to those of excised patches when 1 mM chloride is perfused. Interestingly, delta-Csa appears unaffected by changes in chloride concentration. Since changes in chloride levels also shift Vh levels (indicative of prestin state distribution change), we tested whether increases in patch membrane tension, which shifts Vh to positive levels, is associated with changes in delta-Csa. It is not. These observations indicate that although chloride and membrane tension control Vh (thus, prestin state distribution) an expected change in delta-Csa is absent, and the parameter is not intrinsically dependent on the number of active prestin dimers, where N= Qmax/(z*e-). Boltzmann characteristics are also evaluated at frequencies of 2, 4 and 8 kHz. Delta-Csa, while variable, remains between 20 and 35 fF across frequency in our patches, with Qmax ranging between 15 and 22 fC at 1 kHz. Qmax and z roll off in frequency for all recording conditions, with Qmax decreasing by 8.3 dB from 1 to 8 kHz for on-cell conditions, like our previous macro-patch measures (Santos-Sacchi et al., JNeuro, 2023).

Conclusion: Most evaluations of prestin properties have been garnered with whole cell patch clamp, for example, we estimated sub-membranous chloride to be less than 10 mM by leveraging the relationship between prestin's salicylate sensitivity and whole cell chloride levels (Santos-Sacchi et al., JNeuro, 2006). Our new data indicate levels near 1 mM chloride, and suggest that the sub-plasmalemmal space between the lateral membrane and subsurface cisternae is tightly buffered by the high density of prestin, an anion transporter, within the lateral plasma membrane.

CHROMOSOME ENGINEERING TO RESTORE EUPLOIDY IN CELLS HARBORING A COMPLEX REARRANGEMENT OF CHROMOSOME 8

Lee SN, Qiao L, Thompson SL, Hagenson RA, Davoli T, Sheltzer JM

Introduction: Chromosomal rearrangements on the short arm of chromosome 8 cause 8p syndrome, a rare developmental disorder characterized by neurodevelopmental delays, epilepsy, and cardiac abnormalities. While significant progress has been made in managing the symptoms of 8p syndrome and other conditions caused by large-scale chromosomal aneuploidies, no therapeutic approach has yet been demonstrated to target the underlying disease-causing chromosome.

Methods: Missegregation events were induced in patient derived iPSCs using the Mps1 inhibitor AZ3146, and CRISPR based methods such as KaryoCreate. Single cell colonies were derived and their resulting copy number determined via TaqMan. RNAseq was performed on the revertant clone to identify differentially expressed genes.

Results: After treating the proband line with Mps1 inhibitor AZ3146, we were able to isolate a clone trisomic for chromosome 8, having gained an additional unrearranged copy.

KaryoCreate, a method of inducing chromosome specific missegregation, was then applied to this trisomic line. We were then able to isolate a clone that had lost the rearranged copy of Chromosome 8 and disomic for the unrearranged copy.Transcriptomic analysis of our generated isogenic revertant line and the original 8p syndrome proband line revealed 361 differentially expressed genes between the proband and the euploid revertant, highlighting genes both within and outside the 8p region that may contribute to 8p syndrome pathology.

Conclusion: Here, we establish a two-step approach to eliminate the abnormal copy of chromosome 8 and restore euploidy in cells derived from an individual with a complex rearrangement of chromosome 8p. Our work demonstrates the feasibility of using chromosome engineering to correct complex aneuploidies in vitro and suggests a potential therapeutic avenue for disorders caused by chromosomal rearrangements.

DISCOVERY OF A MISCHARACTERIZED COMPOUND THAT SELECTIVELY TARGETS DRUG-RESISTANT CANCERS

*Debanjan Bhattacharjee, Kaitlin Long, Luciano Romero, Jason Sheltzer**

Introduction: Chemotherapy is a cornerstone of cancer treatment that has been shown to significantly extend patient survival. However, resistance to chemotherapy remains a major challenge in achieving long-term remission. One key mechanism of resistance is the upregulation of the MDR1 (Multidrug resistance 1) efflux pump, which reduces intracellular drug accumulation and decreases sensitivity to a wide range of structurally unrelated chemotherapeutic agents. Therefore, overcoming MDR1-mediated resistance is essential for improving the efficacy of many standard chemotherapy regimens.

We discovered that PAC-1, a mischaracterized caspase-3 activator, exhibits unexpected selectivity for cells overexpressing the MDR1 efflux pump. PAC-1 was originally developed as an activator of the apoptotic enzyme caspase-3 and is currently being evaluated in four clinical trials. However, we found that caspase-3-knockout cancer cell lines displayed similar sensitivity to PAC-1 as control clones expressing caspase-3, suggesting that PAC-1 induces cell death through a caspase-3-independent mechanism.

Methods: To investigate PAC-1's true mechanism of action, we analyzed drug screening data from the Broad Institute's PRISM project. PAC-1's sensitivity was evaluated in multiple in vitro models and isogenic CRISPR-knockout cell lines. Additionally, we performed several iron assays to assess PAC-1's interaction with iron.

Results: Analysis of the PRISM dataset revealed that PAC-1 functions as an iron chelator and that the strongest predictor of PAC-1 sensitivity is high MDR1 expression. Our in vitro and isogenic CRISPR-knockout experiments confirmed that PAC-1 is more effective against cells expressing high levels of MDR1.

Furthermore, in a mixed population of chemotherapy-resistant and chemotherapy-sensitive cells, PAC-1 selectively eliminated the chemotherapy-resistant subpopulation. Mechanistically, we found that PAC-1 is an MDR1 substrate and that MDR1 enhances PAC-1-mediated iron depletion in cancer cells with high MDR1 expression, ultimately leading to iron starvation and cell death over time.

Conclusion: This study provides new insights into the unique mechanism of action of a mischaracterized anticancer agent. MDR1-driven drug resistance remains a significant clinical challenge, and there are currently no validated therapeutic strategies to target MDR1-overexpressing tumors. Our findings suggest that PAC-1 represents a potential novel approach to overcoming drug resistance, addressing a critical unmet need in oncology.

CDK11 INHIBITION IN CANCER THERAPY: EVALUATING EFFICACY, TOXICITY, AND POTENTIAL FOR CLINICAL APPLICATION

Lisa Thomson, Linda Julian, Devon Lukow, Aditi Swamy, Jason Sheltzer

Introduction: CDK4/6 inhibitors cause remarkable tumor regression with minimal toxicities and are now FDA-approved for the treatment of ER+, HER2- breast cancer, prompting efforts to identify additional CDK inhibitors as potential cancer therapies. Recent work from the Sheltzer lab identified the first selective CDK11 inhibitor (OTS964) and revealed a genetic point mutation (CDK11-G579S) that confers resistance to OTS964.

Methods: This study examines CDK11 as a therapeutic target using OTS964 and its derivative, MEL-495R. Wild-type and G579S cancer cell lines were analyzed for proliferation and survival, while RNA sequencing assessed changes in alternative splicing and DNA repair. Public datasets were evaluated for 1p36 deletions, and CRISPR-Cas9 was used to generate 1p36-deleted cancer cells to determine their sensitivity to CDK11 inhibition.

To assess toxicity, a genetically engineered mouse model harboring the Cdk11b-G568S mutation was developed. Wild-type and G568S mice were treated with CDK11 inhibitors, and body weight and organ function were monitored. Xenograft models were used to evaluate in vivo anti-cancer efficacy, with tumor growth as the primary endpoint.

Statistical testing was determined using unpaired t-tests with p-vales <0.05 considered significant.

Results: Our findings demonstrate that CDK11 kinase activity is essential for cancer cell viability and plays critical roles in alternative splicing and DNA repair. Notably, we discovered that chromosomal deletions in the 1p36 locus, which encodes CDK11A, CDK11B, and Cyclin L2, confer sensitivity to CDK11 inhibition. Thus, segmental deletion of 1p36 can be used as a biomarker to predict sensitivity to CDK11-targeted therapies. To evaluate the safety profile of CDK11 inhibitors, we used a genetically modified mouse model harboring the mouse equivalent of the resistance-conferring mutation (Cdk11b-G568S).This model allows us to differentiate between on-target and off-target toxicities. Following CDK11 inhibition, wild-type mice exhibit weight loss and multi-organ dysregulation which is rescued in Cdk11b-G568S mice suggesting that CDK11 inhibition induced substantial on-target toxicity. Finally, tolerable doses of CDK11 inhibitors do not result in significant anti-cancer activity in vivo.

Conclusion: This work shows that CDK11 inhibition is critical for cancer cell viability. However, the on-target toxicity of CDK11 inhibitors is substantial and may limit their clinical application. This extensive and rigorous study highlights the importance of understanding the safety profile of novel cancer therapeutics. It is crucial to identifying potential toxicities, optimize dosing strategies, and ensuring that the benefits of treatment outweigh the risks for patients in clinical settings.

IN-VIVO RESULTS USING A NOVEL NAMPT INHIBITOR (ATN-940) AND EXPLORING THE POTENTIAL FOR NANOPARTICLE ENHANCED DRUG DELIVERY IN RHABDOMYOSARCOMA

Rehman S., Kim A., Bhardwaj P., Lucas K., Cowles RA., Christison-Lagay E., Stitelman D., Vasquez JC

Introduction: Rhabdomyosarcoma is the most common soft tissue malignancy in children. Through the Warburg effect, cancer cells are inherently dependent on NAD+ due to increased reliance on glycolysis for ATP. Nicotinamide adenine dinucleotide (NAD+) depletion via inhibition of nicotinamide phosphoribosyltransferase (NAMPT), a key enzyme in NAD+ production, is an intriguing therapeutic option. Historically, clinical translation has been limited by dose limiting toxicities such as thrombocytopenia and evidence of retinal toxicity in animal models. Prior studies have attempted to mitigate toxicity by supplementing non-tumor cells with nicotinic acid to be utilized to regenerate their NAD+ levels via conversion using a nicotinate phosphoribosyltransferase (NAPRT) dependent pathway. Prior Yale and NIH COG TMA data suggests there is a subset of rhabdomyosarcoma patients that lack NAPRT. Our study utilizes ATN-940, a novel NAMPT inhibitor, that has an improved safety-toxicity margin including lower retina exposure. We also explore the potential for targeting drug delivery with the use of nanoparticles.

Methods: The cell lines used for this study were wild-type NAPRT negative RH41 (RH41 WT) and a NAPRT positive model created by plasmid transfection of a NAPRT overexpression gene into RH41 (RH41 OE). Orthotopic rhabdomyosarcoma models were created by injecting the hind leg of Fox Chase SCID mice with 2 million cells per injection. Mice were randomized into 3 treatment groups: 3mg/kg ATN 940 + 25 mg/kg NA BID, 3mg/kg ATN 940 alone, or control (3% DMSO + 20% captisol). For investigation of nanoparticle distribution, PLGA particles loaded with Di-I (a fluorescent lipophilic dye) were administered by either tail vein injection or direct tumor injection and the distribution of Di-I was assessed using confocal microscopy at 24 hours.

Results: Treatment with ATN-940 abrogated tumor growth in rhabdomyosarcoma. The combination of ATN-940 and nicotinic acid supplementation retained its anti-tumor efficacy in RH 41 WT. In RH41 OE, used here to simulate non-tumor cells with intact NAPRT, ATN-940 had no effect on cell proliferation. Neither tail vein injection nor direct tumor injection of Di-I containing nanoparticles showed cargo delivery in the retina or bone marrow. Direct tumor injection resulted in improved cargo delivery compared to tail vein injection.

Conclusion: ATN-940 plus nicotinic acid is effective in NAPRT negative rhabdomyosarcoma. The potential for nanoparticle encapsulation of NAMPT inhibitors to address the retinal and bone marrow toxicity seen in older generation NAMPT inhibitors warrants further investigation.

HETEROGENEOUS CARDIAC-DERIVED AND NEURAL CREST-DERIVED AORTIC SMOOTH MUSCLE CALLS EXHIBIT SIMILAR TRANSCRIPTIONAL CHANGES AFTER TGFB SIGNALING DISRUPTION

Pengwei Ren, Bo Jiang, Abdulrahman Hassab, Guangxin Li, Wei Li, Roland Assi, George Tellides

Introduction: Smooth muscle cells (SMCs) of cardiac and neural crest origin contribute to the developing proximal aorta and are linked to disease propensity in adults.

Methods: We analyzed single-cell transcriptomes of aortic SMCs from adult mice to determine basal states and changes after disrupting TGFβ (transforming growth factor-β) signaling necessary for aortic homeostasis.

Results: A minority of Myh11 lineage-marked SMCs differentially expressed genes suggestive of embryological origin. Additional analyses in Nkx2-5 and Wnt1 lineage-marked SMCs derived from cardiac and neural crest progenitors, respectively, showed both lineages contributed to a major common cluster and each lineage to a minor distinct cluster. Common cluster SMCs extended from root to arch, cardiac subset cluster SMCs from root to ascending, and neural crest subset cluster SMCs were restricted to the arch. The neural crest subset cluster had greater expression of a subgroup of TGFβ-dependent genes. Nonetheless, conditional deletion of TGFβ receptors resulted in similar transcriptional changes among all SMC clusters. Several disease-associated transcriptional responses were comparable among SMC clusters in a mouse model of Marfan syndrome aortopathy, while many embryological markers of murine aortic SMCs were not detected in adult human aortas.

Conclusion: There are multiple subtypes of cardiac-derived and neural crest–derived SMCs with shared or distinctive transcriptional profiles; neural crest subset cluster SMCs with increased expression of certain TGFβ-inducible genes are not spatially linked to the aortic root predisposed to aneurysms from aberrant TGFβ signaling; and loss of TGFβ responses after receptor deletion is uniform among SMC clusters.

CONSENSUS MOLECULAR SUBTYPE SPECIFIC DRUG SENSITIVITIES IN COLORECTAL CANCER: NEW INSIGHTS FOR PERSONALIZED HIPEC STRATEGIES

Princy Gupta, Elizabeth Godfrey, Kurt Schultz, Lu Qiao, Michael Foote, John Paul Shen, Ardaman Shergill, Michael Cecchini, Raghav Sundar, Jason Sheltzer, Kiran Turaga

Introduction: While cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) has emerged as a promising approach for colorectal cancer (CRC) patients with peritoneal metastases (PM), its effectiveness remains variable. Given the predominance of Consensus Molecular Subtype 4 (CMS4) in CRC-PM, characterized by prominent transforming growth factor β activation, stromal invasion, and angiogenesis, we hypothesized that CMS4 exhibits distinct drug sensitivities compared to other subtypes.

Methods: Drug sensitivity data from the DepMap PRISM Repurposing Dataset for 34 CRC cell lines, classified into CMS subtypes, was analyzed. Five drugs were selected for analysis: mitomycin-C, oxaliplatin, irinotecan, 5-fluorouracil and cisplatin. Differential drug response among CMS subtypes was assessed using log2 fold change (log2FC) in cell viability, with values less than -1.74 indicating sensitivity, based on the sensitivity threshold established in a prior study.

Results: The 34 CRC cell lines were classified as 29% CMS1, 18% CMS2, 26% CMS3, and 26% CMS4. CMS4 cell lines demonstrated higher sensitivity than CMS2 lines to mitomycin-C (mean log2FC = -2.77 vs -0.66, $p = 0.019$) and irinotecan (mean log2FC = -2.26 vs -1.00, $p = 0.03$). Among the drugs tested in CMS4, only mitomycin-C and irinotecan met the sensitivity threshold (log2FC < -1.74), while oxaliplatin did not show sensitivity in this subtype (Figure).

Conclusion: CMS4 exhibits distinct drug sensitivity patterns, which may explain the success of mitomycin-C and limited efficacy of oxaliplatin in HIPEC trials. Future clinical trials should consider genomic subtyping and drug sensitivity testing to guide personalized HIPEC strategies for patients with CRC-PM.

DEFICIENCY OF ATP-GATED P2X7 RECEPTORS CAN CAUSE HYPERACUSIS AND INCREASE SUSCEPTIBILITY TO NOISE

Liang C., Zhai TY., Chen J., Yu N., Zhao HB

Introduction: Type II auditory nerves and the cochlear efferent system constitute a negative feedback loop to control outer hair cell electromotility and hearing sensitivity, which plays a critical role in the protection from noise trauma. However, little is known about the underlying channel mechanisms of this negative feedback loop, particularly the channel function in type II spiral ganglion neurons. Here, we report that ATP-gated P2x7 receptor has predominant expression in the cochlear efferent system and type II spiral ganglion neurons and is required for the cochlear efferent system function; deficiency of P2x7 increases susceptibility to noise.

Methods: P2x7 knockout mice (Stock Number, #005576, The Jackson Lab) were used. The cellular expression of P2x7 in the cochlea was examined by immunofluorescent staining with confocal microscopy. The susceptibility to noise was assessed by exposure to 98-100 dB SPL white noise for 2 hours, one time. Hearing function tests were also examined by ABR and DPOAE recordings. Acoustic startle response (ASR) was also recorded to assess animal behavioral changes. Outer hair cell (OHC) function was assessed by patch clamp recording.

Results: Immunofluorescent staining demonstrated that ATP-gated P2x7 receptor had a predominant expression at type II auditory nerves and lateral olivocochlear (LOC) and medial olivocochlear (MOC) efferent nerves. The intense labeling was detected in the type II spiral ganglion neuron's soma and nerve fibers. The intensive labeling also was visible at the MOC and LOC synaptic areas under OHCs and inner hair cells, respectively. Knockout (KO) of P2x7 increased sensitivity to sound stimulation measured by ASR. ABR and cochlear microphonics (CM) were increased. OHC electromotility associated nonlinear capacitance (NLC) was increased and Vpk of NLC was shifted to left hyperpolarization side. P2x7 KO mice are also susceptible to noise. After exposure to 98-100 dB SPL white noise for 2 hours, ABR thresholds of wild-type mice completely recovered at post-exposure day 7 (P7), whereas P2x7 KO mice retained ~40 dB SPL threshold shift at P7 and had 20-40 dB SPL of permanent threshold shift (PTS) at P28.

Conclusion: These data demonstrated that ATP-gated P2x7 receptors have a critical role in the type II spiral ganglion neurons and cochlear efferent system; deficiency of P2x7 receptors leads to reducing negative control of the cochlear efferent system, therefore increasing hearing sensitivity and susceptibility to noise.

PROMOTION OF NEW CONNEXIN GENE EXPRESSION IN THE COCHLEA AFTER DELETION OF CX26 (GJB2)

Zhai TY., Chen J., Liang C., Kong Y., Zhao HB

Introduction: Connexin 26 (Cx26, GJB2) mutations induce a high incidence of hearing loss, responsible for 70-80% of nonsyndromic hearing loss in children. However, the genetic changes after deficiency of Cx26 remail largely unclear, which hampers to fully understand the underlying deafness mechanisms and develop therapeutic interventions. In this study, we investigated the genetic changes in the cochlea after deletion of Cx26.

Methods: Cx26 knockout (KO) transgenic mice were used. The mouse cochlea was collected. Bulk Poly(A) RNA Sequencing and immunofluorescent staining were performed to assess gene expression changes in the cochlea after Cx26 deletion. Hearing function tests were also examined by ABR and DPOAE recordings.

Results: RNA-Seq examination demonstrated that deletion of Cx26 caused lots of genes up-regulation and down-regulation in the cochlea. In particularly, Cx46 (GJA3), which is an “eye” connexin gene and normally expresses in the eye but not in the ear, had a remarkable upregulation and was newly expressed in the cochlea after deletion of Cx26. Immunofluorescent staining confirmed that Cx46 had expression in the cochlea and occurred at the original places of Cx26 expression. Such new expression of Cx46 also occurred in the Cx26 heterozygous deficient mice. Moreover, this promotion of new connexin gene expression is Cx26-specific. Deletion of Cx30 (GJB6), which co-expresses with Cx26 in the cochlea, could not promote Cx46 expression in the cochlea.

Conclusion: These data demonstrated that Cx26 deficiency could promote new connexin gene expression for compensation. This may provide a useful cue for developing a therapeutic approach for this common hereditary deafness.

THE TRANSFECTED EFFICIENCY OF DIFFERENT AAVS IN THE MOUSE COCHLEA IN GENE THERAPY

Chen J., Lu XL., Yu YD., Zhai TY., Liang C., Zhao HB

Introduction: The virus AAV-based gene therapy currently is the predominant method used in genetic interventions for different diseases, including hearing losses. Different AAV subtypes have different cell- and tissue-specific targeting. However, the knowledge about the transfected efficiency and cell specificity of AAVs in the cochlea is limited; the reported results also appeared confused and contradictory, which has hampered to apply the efficient gene therapies in the auditory system. In this study, we have systematically examined the transfected efficiencies of most used AAVs in the cochlea to provide important and also required information for efficient performance of gene therapy in the hearing system.

Methods: Commonly used AAV1, AAVie, and AAV-Anc80L65 with different promotors were tested. The AAV with eGFP or mNeonGreen were micro-injected into the right cochlea via the posterior semicircular canal (PSCC) route. After 7, 14, and 30 days, the cochlea samples were collected, and the transfection was examined by confocal microscopy. The transfected efficiency was also measured by digital PCR (dPCR). In some mice, acoustic startle response (ASR), ABR, and DPOAE were also recorded to assess animal hearing function and hearing behavioral changes.

Results: First, we found that the transfected efficiency of AAV was largely determined by promotors. For the same AAV subtype, the transfected efficiency could be various largely with using different promotors, from almost 100% to near 0%. Second, the specificity of cell-targeting of transfection was also largely dependent on the used promotors. The difference of transfection efficiency among different AAV subtypes was visible, but less than that with different promotors. Third, the transfected efficiency was also dependent on the injection time. There were different transfected efficiencies and targeted cell types between newborn pups and adult mice. Finally, there was the cross-talking between the right (injection) ear and the left ear. The AAV transfection could be detectable in the left ear, in particularly, as the injection was performed in pups.

Conclusion: The AAV transfection efficiency and specificity of cell-targeting in the cochlea are dependent not only on AAV subtypes but also on promotors.

YALE SURGERY RESEARCH DAY 2025

CLINICAL SCIENCE ABSTRACTS

CHARACTERISTICS AND OUTCOMES OF TYPE A AORTIC DISSECTION REPAIR IN WOMEN

Parekh H., Nasir A., Hassab A., Assi R.

Introduction: Women are reported to have higher in-hospital mortality after thoracic aortic surgery compared to men. This study describes the outcomes in women who underwent surgery for acute Type A aortic dissection (TAAD).

Methods: Electronic medical records were reviewed for women undergoing urgent or emergent TAAD repair from 2013 to 2022 at an aortic center.

Results: A total of 62 female patients underwent urgent or emergent TAAD surgery between 2013 and 2022. Mean age at time of surgery was 66±14.1 years. 73% of the patients were white (n=45/62). Most common comorbidities included hypertension (90%, n=56/62), tobacco use (45%, n=28/62), dyslipidemia (35%, n=22/62), and known pre-existing thoracic aortic aneurysm (29%, n=18/62). 87% of patients (n=54/62) presented with chest pain. 21% presented with a neurological deficit. Operative mortality was 8% (n=5/62). There were no factors significantly associated with operative mortality. The age at time of surgery was associated with increased 1-year mortality, while chronic hypertension was associated with decreased 1-year mortality. There were no variables associated with 30-day composite outcome, which included mortality, reoperation, post-op stroke, post-op dialysis, or post-op bleeding requiring re-exploration.

Conclusion: In this single aortic center study of women undergoing surgery for acute type A aortic dissection, we noted a low prevalence of pre-existing aortic aneurysm (29%, n=18/62) and operative mortality was low. Increased age at time of surgery was associated with increased 1-year mortality, while hypertension was associated with decreased 1-year mortality.

TREATMENT SEQUENCE TRENDS AND PREDICTORS OF PATHOLOGIC UPSTAGING IN TRIPLE NEGATIVE BREAST CANCER

Merkel SK., Lindsay ME., Valero MG., Proussaloglou EM., Greenup RG., Pusztai L., Berger ER.

Introduction: Clinical trials have demonstrated benefits of neoadjuvant chemotherapy in triple negative breast cancer (TNBC) including de-escalation of surgery and assessment of tumor biology to guide adjuvant therapy. The National Comprehensive Cancer Network (NCCN) recommends NAC for larger tumors or nodal involvement. We sought to determine the treatment sequence among TNBC patients who met NCCN eligibility criteria for NAC and identify characteristics associated with pathologic upstaging after upfront surgery, reflecting a missed opportunity for preoperative therapy.

Methods: A retrospective cohort study was conducted using the National Cancer Database. Women, ages 18-89, diagnosed with TNBC between 2010-2020 with a clinical stage T1-3, N0-3, M0 were included. We used descriptive statistics to report patient demographic and treatment trends. Subset analyses included women with cT<2 cm, N0 tumors who underwent upfront surgery to determine what proportion of patients pathologically upstaged based on tumor size and/or nodal status.

Results: 141,546 women were included in the analysis, of which 81,960 (57.9%) underwent upfront surgery and 59,586 (42.1%) underwent NAC. Among those who underwent surgery first, 85.5% met NCCN eligibility criteria for consideration of NAC; majority of which were cT1cN0 tumors. Most women eligible for NAC but who underwent upfront surgery instead were older. There was an increase in use of NAC over the study period (2010-2020). The subset analyses of women with clinical stage cT<2 cm included 46,004 patients who underwent upfront surgery, of which 5.6% were pathologically upstaged based on tumor size and/or nodal status. The majority of these patients (77.5%) were pathologically upstaged from cN0 to pN+.

Conclusion: 85% of women who underwent surgery first met NCCN criteria for receipt of NAC. Pathologic upstaging in the breast and axilla further presented a missed opportunity for NAC among an additional 5.6% of patients. Consistency in eligibility criteria and clinical or radiographic staging may provide standardization around receipt of preoperative systemic therapy.

RISK OF RECURRENCE AND SECOND PRIMARY ANALYSIS AMONG OLDER WOMEN WITH A HISTORY OF BREAST CANCER

Epstein E., Long JB., Lindsay ME., Sheffrin M., Richman IB., Berger EB.

Introduction: Current guidelines recommend annual surveillance mammography for women with a history of non-metastatic breast cancer. The goal of surveillance mammography is to detect second primary breast cancers and in-breast recurrence. However, whether surveillance mammography benefits older women is less clear. Older women with a higher risk of developing a second primary breast cancer or recurrence may benefit most from surveillance. Therefore, the goal of this study was to quantify risk of a second primary breast cancer and recurrence among older women with breast cancer to inform surveillance strategies.

Methods: This is a longitudinal cohort study using data from the SEER-Medicare database. SEER-Medicare links cancer registry data with Medicare claims. The population group includes women who were ages 67 to 100 when first treated for a non-metastatic breast cancer and who were continuously enrolled in Medicare fee-for-service parts A & B beginning 24 months prior to initial breast cancer diagnosis. Using cancer registry data and Medicare claims, we identified cumulative incidence of second primary breast cancers as well as recurrence. We stratified our analysis by age, characteristics of the initial breast cancer, and comorbidity to develop personalized risk estimates.

Results: We found that the risk of a second primary breast cancer was higher among women who were younger, had few comorbidities, and had early-stage cancer at the time of initial diagnosis and lower among those who were older and had more advanced cancer at diagnosis. Risk varied up to 5-fold from 2% to 10% according to age, comorbidity, and stage at diagnosis. By contrast, risk of recurrence was highest among those with advanced cancer at diagnosis and remained considerable even among older women diagnosed at advanced age and with significant comorbidity. Risk of recurrence varied more than 10-fold from 3% to 57%.

Conclusion: Among older women ages 67 to 100, risk of breast cancer recurrence was higher than risk of a second primary breast cancers. Younger women within this cohort and those with fewer comorbidities were at higher risk of both recurrence and diagnosis of a second primary breast cancer. Women with the initial breast cancer diagnosed at an earlier stage had greater incidence of a second primary while those with later stage breast cancer had higher incidences of recurrence.

SMOKING STATUS IN THE U.S. CANCER POPULATION - A NEW PERSPECTIVE OF THE NATIONAL CANCER DATABASE

Giorgio Caturegli, Xuan Zhu, Bryan Palis, Timothy W Mullett, Benjamin J Resio, Daniel J Boffa

Introduction: Historically, approximately 20% of cancers diagnosed in the United States are attributed to tobacco smoking. Smoking impacts both tumor behavior and treatment safety and efficacy. In 2023, the National Cancer Database (NCDB) began collecting smoking status, which we here characterize for the U.S. cancer population.

Methods: Starting in 2023, smoking status was collected by data specialists at Commission on Cancer-accredited hospitals for the NCDB. Patient sociodemographic characteristics were compared by the Chi-squared test using SAS (SAS Institute Inc., Cary, NC, USA).

Results: Among 1,596,789 patients diagnosed with cancer in 2023 and recorded by the NCDB, smoking status was ascertained for 1,546,747 (96.8%). Overall, 47.3% of patients had a smoking history, including 14.7% smoking at the time of their diagnosis. Positive smoking history varied by cancer type, the highest being lung cancer (84.5%) and the lowest thyroid cancer (29.8%). Overall, 70.5% of Asian cancer patients had never smoked, while only 42.6% of American Indian/Alaskan Native patients were never smokers. Rates of current smoking at time of cancer diagnosis varied by sex, age, and race; for example, 18.9% of non-Hispanic Blacks vs. 15.2% of non-Hispanic Whites. Current smoking also varied by socioeconomic characteristics, such as median income: 22.1% in the lowest quartile vs. 9.7% in the highest ($p<0.0001$).

Conclusion: Smoking status was added to the NCDB for over 96% of patients diagnosed with cancer in 2023. The availability of smoking history should enhance opportunities to learn from the NCDB, as tobacco smoking may affect patient treatment and outcomes, and provides a critical adjustment opportunity. The ability to characterize the subset of current smokers is also key, since considerable evidence supports an association between ongoing smoking and detriments to the safety and effectiveness of cancer treatment, as well as increased risks of recurrence and long-term mortality. This early experience with the new smoking variable in the NCDB further suggests that the relationship between tobacco smoking and cancer may vary across sociodemographic and socioeconomic strata. The NCDB could be an important platform to begin to understand these disparities and identify opportunities to address availability and compliance with smoking cessation programs.

IMPROVEMENTS IN STAGE IV NON-SMALL CELL LUNG CANCER SURVIVAL DIFFER BY RACE IN US

Oluwaseun F. Ayoade, Maureen E. Canavan, So Yeon Kim, Daniel J. Boffa

Introduction: The past decade has brought numerous ground-breaking innovations which have redefined the management of stage IV non-small cell lung cancer (NSCLC). However, access to medical innovations has historically been variable across the United States population, which may affect the rate at which patient outcomes improve.

Methods: Patients diagnosed with and treated for Stage IV NSCLC between 2010 and 2020 in the National Cancer Database were studied in 3 eras (2010 - 2013, 2014 - 2017, and 2018 - 2020). Unadjusted survival was assessed by Kaplan Meier and stratified cox analysis was performed to evaluate differences in survival by race and ethnicity.

Results: Overall, 374,273 patients were identified. The median survival was highest across all 3 eras for Asians (12.9, 17.0, and 22.5 months) and the lowest for American Indians/Alaskan Natives (6.9, 6.9, and 9.0 months). Survival increased for all racial/ethnicity groups across eras, consistent with the development of novel therapeutics, but with considerable differences in the proportionality of gains. For example, between era 1 and 3, Hispanics experienced an 81% increase in median survival, while American Indians/Alaskan Natives experienced a 30% increase. Multivariable Cox models also demonstrated considerable variability in mortality risk over time, favoring groups other than non-Hispanic white patients with the exception of American Indians/Alaskan Natives.

Conclusion: There has been a dramatic improvement in survival among stage IV NSCLC over the past decade across all race and ethnicity. The rates of improvement in survival was observed to differ across sociodemographic groups, with the Hispanic patients experiencing the highest benefit. Further studies to understand variability in survival gains by type of therapy or by mutation status are warranted to understand the long-term potential disparities in cancer-related mortality.

IDENTIFYING NON-SYNDROMIC NICU PATIENTS WHO MAY BENEFIT FROM SCREENING FOR HEPATOBLASTOMA

Hellmann ZJ, Rehman S, Thaxton C, Vasquez JC, Solomon DG, Christison-Lagay ER

Introduction: Hepatoblastoma has a low annual incidence (1.7/1,000,000 children), posing a barrier to identifying patients with the disease. It is current standard practice to screen patients with known associated syndromes. Neonatal intensive care unit (NICU) interventions, including total parental nutrition (TPN) and mechanical ventilation, have been shown to be associated with development of hepatoblastoma. We hypothesized that a predictive model could be developed to identify non-syndromic patients that would benefit from screening.

Methods: Pediatric Health Information System data was queried for all NICU admissions with dates of birth between 2016-2022. From this set, duration of use of TPN and mechanical ventilation were determined. Primary outcome was diagnosis of hepatoblastoma in patients admitted between 2016-2023. The dataset was partitioned into two cohorts of equal size, one for training and the other for validation. Least absolute shrinkage and selection operator (LASSO) logit analysis with cross-fold validation was performed on the training sample to develop a predictive model for hepatoblastoma. This model was then tested on the validation cohort.

Results: 258,929 patients met inclusion criteria, with 51 patients diagnosed with hepatoblastoma. Duration of TPN, duration of mechanical ventilation were the retained predictors within the training sample following LASSO logit analysis. Using these retained predictors within the validation sample, the predictive model was found to have excellent discrimination (AUC 0.86) and overall model fit (Brier Score: 0.0002). Observed to expected ratio was 1.07, indicating good model calibration, with performance of the model as expected. A screening threshold within the training sample was set at a predicted probability of 0.00025. Using the screening threshold within the validation cohort, gave a specificity of 0.98 and sensitivity of 0.35. There were 2,521 patients with a predicted probability of developing hepatoblastoma greater than 0.00025, with 9 patients who developed hepatoblastoma (0.36%).

Conclusion: A cohort of infants were identified as having a risk for the subsequent development of hepatoblastoma, similar to that of patients with known associated syndromes. A predictive model was created to assist in identifying patients who may benefit from screening based on specific NICU exposures.

WHY DID THE CHILDREN CROSS THE ROAD? THE RELATIONSHIP BETWEEN ROADWAY DESIGN AND SEVERE PEDIATRIC TRAUMA IN PEDESTRIANS STRUCK BY MOTOR VEHICLE

Jones, AK., Hellman, ZJ., Bergus, K., Mansfield, A., Mansfield, S., Solomon, DG., Christison-Lagay, ER.

Introduction: Driving speed can be statutorily controlled through speed limits, but also modulated through changes to the built environment. Increasing intersection density has previously been shown to lower driving speeds. This study hypothesized that decreased intersection density would correspond with more severe injuries when children were struck by motor vehicles.

Methods: The Ohio Department of Transportation collision dataset was queried for all pedestrians/cyclists younger than 18, who were struck by a motor vehicle between 2019-2023. Each collision was mapped to a census tract. Intersections and road miles per square mile were derived from the National Walk Index. Individuals identified in the dataset were matched on crash proximity to hospital, age, gender, and date to patients in the Pediatric Health Information System at five pediatric hospitals in Ohio, with a diagnostic code for pedestrian/cyclist struck by motor vehicle. Primary outcome was mean calculated injury severity score (ISS), as derived from ICD-10 diagnostic codes.

Results: There were 2,518 pedestrians struck by a motor vehicle, 440 of whom (17.5%) were successfully matched to encounters at a children's hospital in Ohio. Patients were predominantly male (62.3%), non-white(70.0%), without commercial insurance (82.7%), and with an average age of 10.6 years (SD=4.5). Median calculated ISS was 3 (IQR 1-5), with 33 severely injured patients (7.6%) and four patients who died(0.9%). Multivariate analysis controlling for road miles per square mile, sex, age, race, payor, tract SVI, tract population, crashes related to speed, alcohol or drugs, and crashes occurring at nighttime, demonstrated that for each additional 10 intersections per square mile there was a 2.8% reduction in ISS (IRR 0.972, 95%CI 0.96-.985, Figure 1). Patients struck at night had an ISS 60% higher than those struck during the day (IRR 1.59, 95%CI 1.40-1.82).

Conclusion: We conclude that when child pedestrians are struck by a motor vehicle, low intersection density and nighttime collisions correlate with increased injury severity. This highlights tangible local policy changes—such as, increased crosswalks and roadway designs to slow traffic, which could affect traffic similarly to intersections, and street lighting—that could be implemented to decrease the severity of injuries in struck pediatric pedestrians.

DEVELOPMENT OF HEPATOBLASTOMA IS ASSOCIATED WITH NEONATAL EXPOSURE TO TPN AND MECHANICAL VENTILATION

Thaxton C, Hellmann Z, Rehman S, Brown L, Vasquez JC, Solomon D, Christison-Lagay E

Introduction: Gestational age, low birthweight, and overgrowth syndromes are associated with a diagnosis of hepatoblastoma. Previous studies have drawn mixed conclusions regarding the contribution of other neonatal intensive care unit (NICU) exposures to hepatoblastoma development. We hypothesized that exposure to total parenteral nutrition (TPN) and mechanical ventilation during index NICU admission correlate with development of hepatoblastoma.

Methods: The Pediatric Health Information System (PHIS) was queried for all infants admitted to the NICU between 2016-2022. From this set, patients with a diagnosis code for hepatoblastoma were identified. Pharmacy billing information was used to calculate total number of days of TPN and mechanical ventilation exposure during NICU hospitalization. The primary outcome was diagnosis of hepatoblastoma. A sub-analysis was performed in which patients with hepatoblastoma were randomly matched 1:4 to patients without hepatoblastoma that met both of the following criteria: equivalent gestational age in weeks and birthweight within 100 grams.

Results: A total of 293,681 patients met inclusion with 51 patients carrying a diagnosis of hepatoblastoma. Patients with hepatoblastoma had shorter gestations, lower birth weights, longer exposures to both TPN (0 days vs 30 days) and mechanical ventilation (0 days vs 23 days), and higher rates of TPN-related biliary stasis and retinopathy of prematurity. Multivariable logistic regression found that patients that were exposed at any point to TPN (OR=3.11, 95% CI 1.29-7.53, $p<0.01$) or mechanical ventilation (OR=3.46, 95% CI 1.66-7.21, $p<0.01$) were significantly more likely to develop hepatoblastoma, even when controlling for gestational age, birthweight, and sex.

After matching on gestational age and birthweight, multivariable conditional logistic regression showed a significant increased risk of diagnosis of hepatoblastoma for those with any exposure to TPN (OR=5.26, 95% CI 1.33-20.78, $p=0.02$) or any exposure to mechanical ventilation (OR=3.47, 95% CI 1.25-9.64, $p=0.02$). Similarly, matched conditional logistic regression showed a significant dose response increase in the risk of diagnosis of hepatoblastoma for each additional 10 days of TPN (OR=1.28, 95% CI 1.10-1.50) and mechanical ventilation (OR=1.10, 95% CI 1.02-1.18).

Conclusion: Leveraging the magnitude of the PHIS database to capture patients with a prior NICU stay who subsequently developed hepatoblastoma compared with a matched population of those who did not, we were able to demonstrate a relationship between duration of exposure to mechanical ventilation and TPN and the later diagnosis of hepatoblastoma. Future investigations should be directed at the role these interventions may play in hepatoblastoma oncogenesis.

UTILITY OF PRE-OPERATIVE ULTRASOUND FOR SURGICAL DECISION MAKING IN NEONATES DIAGNOSED WITH NECROTIZING ENTEROCOLITIS

Wilson, EM., Hellmann, ZJ., Haynes, CV, Solomon, DG., Christison-Lagay, ER.

Introduction: When determining timing and need for surgical intervention in neonates diagnosed with necrotizing enterocolitis (NEC), a life-threatening neonatal condition, ultrasonography (US) may provide additional information regarding pneumatosis, portal venous gas, loss of mural stratification, and presence of complex fluid, suggestive of perforation. Traditionally, abdominal x-ray and clinical perturbations, in the absence of pneumoperitoneum, guide surgical decision-making. We hypothesized hospitals with high US utilization would have lower rates of surgical intervention, without compromising on likelihood of mortality in neonates with NEC.

Methods: The Pediatric Health Information System (PHIS) identified patients with an ICD-10 code for NEC born between 2016-2023. Data regarding mortality, surgical intervention, US, mechanical ventilation, and TPN administration were collected. US utilization terciles were defined based on the proportion of children receiving US within 48 hours of exploratory laparotomy (ex-lap) relative to all ex-laps performed at each hospital. Comparisons were made between the lowest and highest terciles, low and high US utilization hospitals, respectively. Primary outcome was progression to surgery; secondary outcome was mortality.

Results: 7903 neonates were diagnosed with NEC in the PHIS NICU dataset between 2016-2023, of which 2004 underwent ex-lap, and 337 received US imaging within 48 hours preceding ex-lap. 30.6% of neonates at high US utilization hospitals had an US within 48 hours preceding ex-lap, compared to just 4.5% for those in the low US utilization hospitals.

Multivariable logistic regression, correcting for gestational age, birthweight, and sex, demonstrated a 27% lower likelihood of undergoing ex-lap for those children admitted to high US utilization hospitals compared to low US utilization hospitals (OR 0.73, 95% CI 0.64-0.84, p =<0.001). Among all children admitted with NEC, those admitted to the high utilization hospitals were no more likely to die during index admission compared to those admitted to low utilization hospitals (OR= 0 .91, 95% CI 0.78-1.06, p = 0.228). There was also no difference in mortality between high and low utilization hospitals following ex-lap for NEC (OR=1.14, 95% CI 0.86-1.48, p =0.306).

Conclusion: Neonates at high US utilization hospitals are significantly less likely to undergo ex-lap for necrotizing enterocolitis. There were no differences in mortality outcomes when comparing kids at high and low US utilization hospitals, which suggests US may be guiding surgical decision-making without compromising on the most dire outcomes. However, additional studies are needed to elucidate how US utilization influences more granular decisions regarding surgical timing and management, and the effect it might have on patient outcomes.

CORRECTED AGE AS A PREDICTOR OF OUTCOMES FOR NEONATES DIAGNOSED WITH NECROTIZING ENTEROCOLITIS RECEIVING EXPLORATORY LAPAROTOMY

Wilson, EM., Hellmann, ZJ., Haynes, CV., Solomon, DG., Christison-Lagay, ER.,

Introduction: Necrotizing enterocolitis (NEC) is a life-threatening neonatal infection, diagnosed clinically, where medical management prioritizes stabilization and preventing progression. Clinical decompensation and intestinal perforation are primary indications for surgery in the absence of pneumoperitoneum. Timing of intervention remains an area of active clinical interest. While metrics such as birthweight are known predictors for post-operative outcomes, the effect of surgical age on outcomes remains undefined.

Methods: The Pediatric Health Information System (PHIS) identified patients with an ICD-10 code for NEC who underwent ex-lap based on billing codes from 2016-2023. Data regarding ultrasound (US), mechanical ventilation (MV), TPN administration, and demographics were collected. Neonates with a known congenital heart defect or insufficient data were excluded from analysis. Durational outcome calculations excluded deceased neonates. Corrected age (CGA) was summed using gestational age (GA; days) and days from birth to ex-lap. Primary outcome was mortality, with secondary outcomes including post-operative length of stay (LOS), TPN and MV duration.

Results: 2004 neonates with NEC underwent ex-lap, of which 514 died. 49.4% (n = 989) of neonates were >218 days (31.1weeks) at time of surgery and 50.7% (n =1015) were <218 days. Neonates <218 days at surgery had significantly lower birthweight (760g v. 1535g, p = <0.001), higher mortality (30.4% v. 20.7%, p=<0.001), longer post-op LOS (127d v. 82d, p=<0.001), TPN (102d v. 63d, p=<0.001), and MV days (82d v. 24d, p=<0.001). Multivariate logistic regression controlling for US within 48-hours of ex-lap, birthweight, bed quartile, and sex identified GA, CGA, and US as significant predictors of post-op LOS, TPN, and MV days, with larger hospitals also (q3,4) contributing to MV days.

Comparing GA to CGA by patient, noting mortality, among the 378 deaths within 2 weeks of ex-lap, 74.3% occurred at < 30 weeks GA and 84.7% of those within the first 4 weeks of life. Comparing GA to age at surgery (weeks), 84.9% of mortality within 2 weeks of ex-lap occurs in the first 4 weeks of life. Irrespective of GA, lower CGA tends to result in higher mortality.

Conclusion: Neonates undergoing ex-lap <218 days CGA had lower birthweight, faster progression to surgery, and higher post-op morbidity and mortality, likely reflecting physiologic immaturity and potentially more severe disease. In contrast, neonates >218 days had lower post-op LOS, TPN days, and MV days, reflecting improved peri-operative outcomes. Corrected age at time of surgery may aid in improved risk stratification and surgical timing optimization to improve prognostication and outcomes in NEC.

THE IMPACT OF HOSPITAL VOLUME ON MANAGEMENT STRATEGY IN THE TREATMENT OF PEDIATRIC EMPYEMA

Haynes CV., Hellmann ZJ., Wilson EM., Solomon DG., Cowles RA.

Introduction: An extensive body of literature led to the development of the American Pediatric Surgical Association (APSA) guidelines for the management of children with empyema. It was hypothesized that centers with fewer empyema patients more frequently deviate from APSA guidelines, potentially leading to poorer outcomes.

Methods: The Pediatric Health Information System (PHIS) was queried to identify patients aged 3-18 with empyema without fistula between 2016-2023. Patients were included if they underwent chest tube placement or video-assisted thoracoscopy (VAT) within 3 days of admission. Patients were excluded if they had diagnoses of abscess, gangrene, or other empyema-related complications, or if they underwent open thoracotomy. 48 hospitals were grouped based upon empyema case volume: low-, medium-, and high-volume. Outcomes were compared between groups using multivariate logistic and Poisson regression models to adjust for potential confounders, including patient demographics and clinical characteristics.

Results: 1,698 patients met inclusion criteria. The average number of empyema cases at low-, medium-, and high-volume hospitals was 23.0(SD7.0), 46.7(SD8.6), and 99.7(SD34.5), respectively. Patients at medium- and high-volume hospitals had 32% (OR=0.68, 95%CI: 0.48–0.96, p=0.041) and 50% (OR=0.50, 95%CI: 0.34–0.75, p=0.001) lower odds of undergoing a chest CT within 3 days of admission. Length of stay was 11.4% (IRR=0.89, 95%CI: 0.80–0.98, p=0.017) and 9.4% (IRR=0.91, 95%CI: 0.82–1.00, p=0.051) shorter at medium- and high-volume hospitals, respectively, while inpatient antibiotic use was reduced by 11.3% (IRR=0.89, 95%CI: 0.82–0.96, p=0.002) and 8.1% (IRR=0.92, 95%CI: 0.85–0.99, p=0.037). No differences were observed in 30-day readmission rates, ICU admissions, or mechanical ventilation use between terciles.

Conclusion: Hospitals with medium and high empyema case volumes demonstrate closer adherence to APSA guidelines, demonstrated by lower rates of chest CT compared to low-volume hospitals. These hospitals also displayed improved efficiency for empyema patients, as evidenced by shorter lengths of stay and fewer antibiotic days. There were no differences in critical outcomes, such as readmission rates, ICU admissions, or mechanical ventilation, to suggest differences in patient severity across terciles. These findings imply that lower-volume centers may benefit from more standardized care pathways. Further research is needed to explore the mechanisms driving these inefficiencies and to determine if similar patterns exist for other complex pediatric surgical conditions.

DECLINING INCIDENCE OF GASTROSCHISIS PARALLEL DECLINES IN MATERNAL SMOKING RATES IN THE UNITED STATES: A DEPARTMENT OF HEALTH AND HUMAN SERVICES POPULATION BASED ANALYSIS

Fortoul, M.C., Hellmann, Z.J., Buu, L., Solomon, D.G., Cowles, R.A.

Introduction: Previous studies have shown that smoking prior to conception and during pregnancy is a risk factor for gastroschisis. Since smoking rates among young adults have declined between 2011 and 2022, we hypothesized that this would be associated with a concurrent decrease in gastroschisis rates among live births in the United States.

Methods: Data were obtained from a publicly available, de-identified dataset released by the U.S. Department of Health and Human Services (HHS) encompassing all live births in the United States from 2017 to 2023. The dose of maternal exposure to cigarettes was included as an independent variable. The primary outcome was a diagnosis of gastroschisis.

Results: A total 25,836,224 live births with complete information were recorded by the HHS between 2017 and 2023. Within this cohort, 5,121 infants (~2:10,000 births) were diagnosed with gastroschisis. Among these, 858 (16.75%) were born to mothers with a history of smoking prior to pregnancy.Annual trends demonstrate a decline in maternal smoking from 9.4% in 2017 to 4.1% in 2023. Concurrently, the incidence of gastroschisis decreased from 2.4 per 10,000 births in 2017 to 1.6 per 10,000 births in 2023. Univariate analysis revealed that infants born to mothers with a history of smoking within three months prior to conception prior to pregnancy were significantly more likely to have gastroschisis (OR = 2.82, 95% CI 2.62–3.04, $p < 0.001$). A dose-response analysis demonstrated that for every additional 10 cigarettes smoked daily prior to conception prior to pregnancy, the odds of a gastroschisis diagnosis increased by 39% (OR = 1.39, 95% CI 1.35–1.43, $p < 0.001$).

Conclusion: Consistent with prior research, these findings confirm a significant association between maternal smoking prior to conception and gastroschisis. Additionally, there was a significant decline in the proportion of mothers who reported smoking within three months prior to conception, which was paralleled by a similar decline in annual gastroschisis rates between 2017 and 2023 among live births in the United States.

INNOVATIONS AND ADVANCES IN ARTERIOVENOUS FISTULA CREATION

Lazcano-Etchebarne C., Aboian, E., Strosberg, D., Sadaghianloo, N., Schwartz, A., Ho, B., Ohashi, Y., Kano, M., Gonzalez, L., Bai, H., Dardik, A.

Introduction: Arteriovenous fistulae (AVF) are the gold standard for vascular access among hemodialysis patients; however, they have high primary failure rates. Novel approaches to improve AVF patency include modifications to open techniques, such as radial artery deviation and reimplantation fistula, and percutaneous approaches like endovascular AVF (endoAVF). Despite these advances, these modifications have limited impact on reducing neointimal hyperplasia, stenosis, or thrombosis, thereby restricting their ability to improve AVF maturation. Emerging strategies, including drug-embedded and bioresorbable perivascular wraps, aim to prevent neointimal hyperplasia. Increased AVF failure rates among women highlight sex differences in AVF biology and suggest additional targets for improvement. Other advancements, such as immune system modulation and stem cell therapies, show promise. While these technologies may enhance AVF maturation, long-term patency and prevention of complications like central vein stenosis and dialysis access steal syndrome remain critical areas for continued innovation.

Methods: This narrative review explores recent innovations in AVF creation. Relevant articles and clinical trials were identified through PubMed, Google Scholar, and ClinicalTrials.gov using search terms such as "arteriovenous fistula," "vascular access," "endovascular techniques," and "hemodialysis access," focusing on studies from the past decade. Clinical guidelines and expert perspectives were also incorporated.

Results:
Innovations in AVF Creation:

- The RADAR and pSLOT techniques improve AVF maturation and patency.
- EndoAVF techniques (Ellipsys, WavelinQ, Velocity) provide minimally invasive options but have strict anatomical requirements and often require secondary interventions.
- Devices like VasQ and Optiflow enhance anastomotic geometry and improve patency.

Challenges in AVF Maturation:

- Neointimal hyperplasia (NIH) is a major cause of AVF failure.Women have higher AVF failure rates due to biological and hemodynamic factors.
- Emerging Therapies to Improve AVF Patency:Drug-eluting wraps aim to reduce NIH.Stem cell therapies and immune modulation show promise in venous remodeling.Paclitaxel-coated balloons and PCSK9 inhibitors are being studied for stenosis prevention.

Complications & Management Strategies:

- Central vein stenosis treatments include angioplasty, stenting, and thoracic outlet decompression.
- Dialysis-associated ischemia is managed via surgical revisions.
- Alternative access options, such as acellular vascular grafts (TRUE AVC™, Humacyte), are being developed.

Conclusion: Advancements in AVF creation, including open and endovascular techniques, expand surgical options. The RADAR technique and endoAVF systems like Ellipsys, WavelinQ, and Velocity continue to refine AVF access. However, challenges in AVF maturation and patency persist. Research into NIH mechanisms may drive paradigm shifts in treatment, and recognition of sex differences may enable personalized, sex-specific interventions. Emerging therapies, advanced monitoring, and computational modeling may further improve AVF outcomes.

AORTIC DISEASE AND SURGICAL INTERVENTION IN BICUSPID AORTIC VALVE PATIENTS: THE ROLE OF FUSION TYPES

Wang K., Erez E., Ramponi F., Di Luozzo G.

Introduction: Bicuspid aortic valve (BAV) cusp fusion types are linked to distinct aortopathies through genetic and hemodynamic factors, yet their impact on disease presentation and surgical treatment remains underexplored. This study compares aortic disease and surgical treatments between BAV patients with right-left and right-noncoronary cusp fusions.

Methods: This observational cohort study evaluated all adult patients in the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) Registry (2007-2016) with a BAV and either right-left (RL) or right-noncoronary (RN) cusp fusions. Patients with a history of either aortic coarctation or tetralogy of Fallot were excluded. Echocardiographic features, surgical intervention rates, surgical indications and types of surgeries performed were compared between the two cusp fusion types.

Results: Of 295 patients, there were 244 patients with RL and 51 with RN fusion types. Females represented 27% of the RL and 35% of the RN group (p=0.21). Median age at diagnosis was 44 years for both subtypes, with no differences in GenTAC Registry enrollment criteria between the subtypes. At enrollment, 94.7% (231/244) of RL and 90.2% (46/51) of RN patients had a diagnosis of thoracic aortic aneurysm, dissection or tortuosity (p=0.50). RL patients showed larger sinus of Valsalva diameters (3.86 cm vs. 3.50 cm, p<0.001), while RN patients had higher rates of aortic stenosis (p=0.007) and greater peak aortic gradients (21 mmHg vs. 15 mmHg, p=0.004) on initial echocardiograms. In the RL group, 136 (56%) patients underwent at least one procedure compared to 23 (45%) in the RN group (p=0.17). The RL group had higher aortic root replacement rates (44% vs. 26%) and higher valve sparing root replacement rates (13% vs. 0%), though these differences did not reach statistical significance (p=0.11 and p=0.14, respectively). Acute aortic syndrome was a common indication for surgery, accounting for 8.1% (11/136) of RL patients requiring surgery and 13.0% (3/23) of RN patients.

Conclusion: RL and RN fusion types in BAV patients show distinct echocardiographic and surgical profiles, suggesting fusion type-specific screening and management could improve outcomes. The high prevalence of acute aortic syndrome in both subtypes warrants further investigation.

THORACIC AORTIC ANEURYSM IN PATIENTS WITH GIANT CELL ARTERITIS

Strachan S., Zafar M., Changez M., Celik NB., Khattack A., Ziganshin BA., Elefteriades JA.

Introduction: Despite increased awareness of Thoracic Aortic Aneurysm (TAA) in Giant Cell Arteritis (GCA) patients, the incidence, predictive factors, role of imaging, and outcomes of aortic complications in this population remain inconsistently reported across studies. This has implications for screening, diagnosis, and management strategies for aortic complications, potentially impacting patient outcomes. We aimed to better define the association between TAA and GCA, thereby enhancing clinical awareness of this life-threatening complication.

Methods: We used a 2-step search approach to the available literature on TAA and GCA. Firstly, databases including PubMed, Web of Science and Embase were searched. Additionally, relevant studies were identified through secondary sources including references of initially selected articles. We conducted a preliminary retrospective study to identify patients at our institution who were diagnosed with both TAA and GCA from January 1980 through December 2024. Descriptive statistics were used to support the association between these two diseases described in the literature.

Results: The literature review disclosed an increased incidence and relative risk of TAA among patients with GCA. GCA patients experienced progressive aortic enlargement, which may be due to vascular inflammation and disruption of elastin and collagen fiber biology in the vessel wall, resulting in mechanical weakness. Predictors of aneurysmal disease included aortic insufficiency and severe inflammatory response at the time of GCA diagnosis, as well as risk factors such as male sex, hypertension, hyperlipidemia, coronary disease, diabetes, and smoking. The investigation at our institution revealed that among 2,373 patients with GCA, 80 developed TAA, an incidence of 3.4%. Among those, 70 (87.5%) had an ascending aortic aneurysm, 5 (6.25%) had a descending aortic aneurysm, and 5 (6.25%) had both. Of these, 37 (46.3%) were male, 74 (92.5%) had hypertension, 49 (61.25%) were former or current smokers, 21 (26.3%) had diabetes mellitus, 73 (91.3%) had hyperlipidemia, 32 (40%) had coronary disease, 34 (42.5%) had concomitant polymyalgia rheumatica, and 22 (27.5%) had aortic insufficiency at the time of GCA diagnosis.

Conclusion: Our study highlights a 3.4% incidence of TAA in GCA patients, with hypertension, smoking, and hyperlipidemia as the most common risk factors. Ascending aortic aneurysms were the most frequent, occurring in 87.5% of cases. These findings emphasize the importance of monitoring for TAA in the GCA population.

EVALUATION OF RADIOGRAPHIC PREDICTORS OF ADVERSE OUTCOMES IN MEDICALLY MANAGED ACUTE TYPE B AORTIC DISSECTION PATIENTS.

Khattak MAN., Zafar MA., Kalyanasundaram A., Ellauzi H., Perez ZG., Ziganshin B., Elefteriades JA.

Introduction: The literature describes several radiographic predictors of adverse outcomes in acute type B aortic dissection patients. We sought to determine the clinical validity of these predictors among patients with medically managed, initially uncomplicated acute type B aortic dissections (free of rupture, ischemia, acute expansion).

Methods: 81 uncomplicated acute type B dissection patients presenting to our institution for management between 1994 and 2021 with a contrast enhanced computerized tomography (CT) scan on file were analyzed. Radiographic features at presentation analyzed for this study included: maximal descending aortic overall diameter, true and false lumen diameters, maximal ascending aortic diameter, dissection origin location (greater vs. lesser curvature), degree of false lumen thrombosis, branch vessel perfusion and true vs false lumen supply of the branch vessels. These factors were reevaluated in serial scans, and descending aortic growth rates were computed. Measurements were done perpendicular to the long axis of the aorta. The two endpoints analyzed in this study included a descending aortic specific endpoint (descending aortic rupture and aorta related mortality), and a composite endpoint (aortic specific endpoint, descending aortic surgery and all-cause mortality). Regression analyses were conducted to determine the factors' association with these endpoints.

Results: Mean age at presentation was 60 years. 48 (59.3%) patients were males and 33 (40.7%) were females. Mean follow up duration (from presentation to an endpoint as defined above) was 4.7 years. Median descending aortic growth rate was 0.41 mm/year. The area of maximal dilatation was in the proximal descending aorta (T1-T6). For the aortic adverse event endpoint no radiographic factor was a significant predictor on univariate regression or multivariate regression. For the composite endpoint maximal descending aorta diameter ($p<0.001$) and true lumen diameter ($p=0.033$) were significant predictors on univariate analysis whereas multivariate analysis showed no significant predictors. The freedom from an aortic endpoint at 12 years was 75%.

Conclusion: We do not confirm prior expectations regarding the value of anatomical variables in prediction of adverse aortic events after acute type B aortic dissection. In patients triaged to optimal medical therapy, ultra long term aortic outlook is more benign than previously anticipated, even in the presence of putative radiographic "high risk' indicators.

ANALYSIS OF ONLINE CROWDFUNDING AMONG PATIENTS PURSUING METABOLIC AND BARIATRIC SURGERY IN THE UNITED STATES

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Introduction: Use of online crowdfunding to mitigate health-related cost burden is common in the US, but its usage among candidates for metabolic and bariatric surgery (MBS) is unknown. We aimed to identify GoFundMe campaigns fundraising for MBS and characterize sources of financial strain. We also aimed to determine factors associated with successful crowdfunding.

Methods: We searched GoFundMe for campaigns fundraising for MBS. Data items were extracted by two investigators with disagreements resolved by a third. We assessed associations between these data items and category of money raised using ordered logistic regression.

Results: We identified 539 campaigns, of which 33.6% were raising funds for sleeve gastrectomy, 24.1% for Roux-en-Y gastric bypass, and 2.0% for biliopancreatic diversion with duodenal switch. Most campaigns were created by the patient (73.1%) who had health insurance (53.4%) and at least one obesity-associated disease (56.8%). Over half (53.6%) sought funds for a direct medical expense and 35.1% sought funds for a non-medical expense, which included lost wages (15.6%), food (10.8%), transportation (10.2%), childcare (7.1%), and/or housing (5.8%). The median requested was $8000 (IQR 10,440) and the median raised was $860 (IQR 3173). The majority (63.1%) of campaigns earned less than 25% of their requested amount. Campaigns that shared mental health-related disease (aOR 0.55, 95% CI 0.32-0.95) and non-surgical attempts to lose weight (aOR 0.59, 95% CI 0.37-0.94) had lower odds of raising a higher category of money compared to campaigns not disclosing these details.

Conclusion: Patients pursuing MBS in the US use online crowdfunding to subsidize both medical and non-medical expenses, but the majority of campaigns are unsuccessful. Our study highlights unmet financial need among MBS candidates.

DECISIVE (DECISIONS AND EXPECTATIONS IN CYTOREDUCTION: INFORMED SURGERY INCORPORATING VALUE EXPLORATION): DEVELOPMENT OF A DECISION SUPPORT TOOL FOR INDIVIDUALS WITH PERITONEAL SURFACE MALIGNANCIES

Godfrey EL, Linhares SM, Hamid SA, Moses J, Lindsay ME, Proussaloglou EM, Berger ER, Valero MG, Shergill A, Turaga KK, Greenup RA

Introduction: Individuals with peritoneal surface malignancies (PSM) considering cytoreductive surgery (CRS) face substantial barriers to informed, value-concordant decision-making. No studies have comprehensively explored decisional needs and priorities for this population and their caregivers.

Methods: The DECISIVE survey comprised 117 items combining validated instruments addressing care experiences and decisional outcomes, and study-specific items exploring decisional and treatment experiences, priorities and needs. The survey was distributed to a convenience sample of three patient advocacy organizations for individuals with appendiceal and colorectal tumors who considered cytoreductive surgery and their caregivers. Quantitative measures were evaluated using descriptive statistics, and free responses assessed with an integrated, inductive and deductive team-based approach.

Results: There were 91 complete and 121 partial survey responses. Of the respondents, 76.0% were people with cancer and the remainder were caregivers of people with cancer. Most people with cancer had appendiceal disease (90.9%) and were female (65.0%) and white (94.2%). Of caregiver respondents, 41.4% reported the person with cancer had died. Difficulty in accessing care was common, with 31.4% reporting their surgeon was over 201 miles away from their residence.Overall, 92% of respondents reported decision satisfaction by the “Was It Worth It” measure, but among caregivers, only 80% reported the decision was “worth it”, and only 68% would make the same decision again. Most (>75%) respondents reported receiving adequate information about the perioperative period, but over half (50.4%) reported their informational needs were not met in terms of descriptive disease and treatment outcomes.
Respondents considered cancer control and survival as most important for their decision-making, followed by quality of life and symptom control. About half of participants reported treatment burden to be important. Emotional symptoms of cancer were most frequently reported as a challenge to decision-making (48.3%), followed by the sense there were no other treatment options (42.0%) and time pressure (40.3%).
Preliminary qualitative analysis of the free-response elements demonstrates a desire for decisional support. Participants desire dietary guidance (n=4); prognostic data based on disease characteristics (n = 8); and guidance to support self-efficacy, including support group contacts, reliable resources, and clear treatment guidelines, particularly to counteract poor quality counseling and medical dismissal that participants reported had led to distress and delayed care (n=8).

Conclusion: DECISIVE has characterized key decisional needs, including specific informational needs and resources, that will allow for the creation of high-quality decision support tools that mitigate barriers to value-concordant decision making for patients and caregivers considering CRS.

A REGISTRY STUDY EXPLORING THE IMPACT OF HEALTHCARE ACCESS AND DISEASE FACTORS ON THE BENEFIT OF HIGH-VOLUME CARE IN EARLY BREAST CANCER

Godfrey EL, Lindsay ME, Thomas SM, Hamid SA, Moses J, Proussaloglou EM, Berger ER, Valero MG, Leeds I, Ramirez A, Gross CP, Greenup RA

Introduction: Regionalization of complex cancer treatment to high-volume centers has increasingly been pursued for cancer care. However, for many patients, there is significant burden associated with accessing high-volume centers in addition to a higher risk of increased time to treatment and care fragmentation. We hypothesize that in common, surgically treated cancers such as breast cancer, these barriers will be associated with decreased strength of the volume-outcome relationship, but certain disease and patient characteristics will strongly favor high-volume care.

Methods: We queried the National Cancer Database for patients diagnosed with early breast cancer from 2007-2017. Using restricted cubic spline methodology, we modeled the relationship between rolling annual breast surgical volume and the natural log of the hazard ratio for adjusted survival, then derived specific thresholds in the relationship between hospital volume and survival. We compared patient, disease, and healthcare access characteristics across the thresholds. Multivariable regressions and subgroup analysis will be performed to identify predictors of utilization of high-volume centers, and patient-level characteristics associated with the greatest benefit of treatment at high-volume centers.

Results: The sample included 308152 people diagnosed with early-stage breast cancer from 2007-2017, 99.2% of whom were female and 74.4% of whom were non-Hispanic white. Restricted cubic spline modeling revealed an inflection point at approximately 205 (95% CI, 159.12-307.44) breast cancer surgeries a year. Below this volume threshold, there is a distinctly stronger association between surgical volume and all-cause survival such that small increases in volume correlate with a a notable increase in natural log hazard of survival, whereas above the threshold, this relationship flattens. People receiving care in the high-volume tier were more likely to be privately insured (59.7% vs 51.0% in low volume) and have no Charlson-Deyo scored comorbidities (84.4% vs 82.7%) than the low-volume tier. We predict there will be patient- and disease-specific characteristics associated with a stronger or weaker volume-outcome relationship relative to this threshold; for example, we anticipate high-risk histologic features or more advanced age may be associated with a stronger survival advantage at high-volume centers than patients without those features.

Conclusion: Efforts to regionalize cancer treatment have primarily focused on the most complex disease presentations, but less is known about how and for whom regionalization should be prioritized in more common early-stage cancers including breast cancer. These methods can be applied to other common early-stage cancers and the findings used to drive further outcomes research and policy interventions for optimal regionalization.

THIRTEEN YEARS OF IMMEDIATE LYMPHATIC RECONSTRUCTION (ILR) FOR THE PREVENTION OF LYMPHEDEMA: A META-ANALYSIS OF PROSPECTIVE CLINICAL TRIALS

Shen Y., Brown S., Klimitz F., Mattia A., Pomahac B., Haykal S.

Introduction: Cancer-related lymphedema is a common and debilitating condition, affecting 20-40% of cancer patients undergoing lymph node dissection. It leads to chronic swelling, severe functional impairments, and irreversible lymphatic damage. There is no cure for lymphedema and current treatments are palliative, prevention is crucial. Immediate lymphatic reconstruction (ILR) using microsurgical techniques during lymph node dissection is a novel preventative technique that mitigates surgical injury before lymphedema develops. Despite the growing use of ILR for preventing lymphedema, prospective long-term data on its efficacy remain limited. This study aims to analyze long-term, prospective outcomes of ILR, utilizing all available outcome measures.

Methods: A systematic review was conducted on PubMed, Embase, and Web of Science to search for studies on ILR to prevent or reduce the incidence of lymphedema in patients undergoing axillary lymph node dissection in accordance with the PRISMA guidelines. Outcome data included the pooled cumulative incidence of lymphedema (assessed by limb measurements), odds ratio (OR), and relative risk (RR) for lymphedema development in patients who underwent ILR versus those who did not. Only prospective clinical trials with a minimum of 12 months of follow-up were included.

Results: Nine prospective studies (2011–2024) were included, totaling 762 patients, with 455 undergoing ILR. The average follow-up was 16.8 ± 5.4 months. An average of 1.9 ± 0.43 anastomoses were performed per patient. ILR was associated with a significantly lower incidence of lymphedema: 12.77% (95% CI: 1.77% – 5.90%) compared to 32.46% (95% CI: 7.11% – 13.97%) in the non-ILR group. Patients who received ILR had 48% lower odds of developing lymphedema compared to those without ILR (OR = 0.52, 95% CI: 0.350 – 0.771, p = 0.0012). A 32% reduction in lymphedema risk was also observed among ILR recipients (RR = 0.68, 95% CI: 0.505 – 0.913, p = 0.0104).

Conclusion: This meta-analysis is the largest study to evaluate the long-term efficacy of immediate lymphatic reconstruction (ILR) in lymphedema prevention. The findings demonstrate that ILR significantly reduces the incidence, odds, and risk of lymphedema, supporting its role as an effective preventive strategy in at-risk patients.

TWO DECADES OF LYMPHOVENOUS BYPASS (LVB) FOR THE TREATMENT OF LYMPHEDEMA: A META-ANALYSIS OF PROSPECTIVE CLINICAL TRIALS

Shen Y., Brown S., Klimitz F., Mattia A., Pomahac B., Haykal S.

Introduction: Cancer-related lymphedema is an incurable, chronic, debilitating and lifelong condition affecting 1 in 3 cancer patients undergoing axillary lymph node dissection. Lymphovenous bypass (LVB) is a promising surgical intervention for the management of cancer-related lymphedema. This condition, resulting from damage to the lymphatic system following cancer treatment, leads to swelling, pain and functional impairment. This significantly impacts patients' quality of life. Despite the increasing use of LVB for lymphedema treatment in recent years, there is a lack of high-level, prospective, long-term data and standardized outcome metrics. The purpose of this study was to analyze the long-term, prospective outcomes of LVB throughout the past two decades using all available outcome measures.

Methods: We conducted a systematic review on PubMed, Embase, and Web of Science to identify prospective clinical trials investigating LVB for lymphedema treatment. Outcome data included limb measurements, cellulitis episodes, compression use, and complications. Only prospective clinical trials with a minimum follow-up duration of 12 months were included. For studies involving multiple procedures, only outcomes from LVB cohorts were analyzed.

Results: Eighteen prospective studies (2004-2024) were included, comprising a total of 1334 patients undergoing LVB with a mean follow-up time of 18.7±10.6 months. An average of 3.0±0.7 anastomoses were performed per patient. LVB was associated with significantly reduced limb volumes with 19.72% (95% CI 18.44-21.82; $p<0.001$), 27.42% (95% CI 26.85-31.05; $p<0.001$) and 29.55% (95% CI 29.05-32.07; $p<0.001$) mean reduction 1, 2 and 3 years after LVB, respectively. Additionally, LVB decreased the total number of cellulitis episodes by 97.0% (95% CI 94.72-98.02; $p<0.001$) and the number of episodes per year by 91.6% (95% CI 90.02-93.09; $p<0.001$). A total of 41.4% of patients discontinued compression garment use following LVB.

Conclusion: This is the largest study to evaluate the long-term safety and efficacy of lymphovenous bypass (LVB), summarizing two decades of prospective experience. LVB is a safe and effective treatment option, yielding durable improvement in limb volumes and cellulitis reduction. LVB is a safe and effective treatment option, yielding durable improvements in limb volumes and reductions in cellulitis episodes. Additionally, LVB facilitates a reduced dependency on compression garments, enhancing patients’ quality of life.

ADVANCING LYMPHEDEMA PREDICTION IN CANCER CARE: THE YALE CANCER CENTER (YCC) MODEL UTILIZING A COHORT OF 15,666 CASES

Brown S, Shen A, Klimitz F, Mattia A, Nair M, Pomahac B, Haykal S.

Introduction: Lymphedema is a common, debilitating condition following lymph node dissection and affecting 1 in 3 breast cancer patients. Current interventions focus on symptom management rather than prevention. There are no models looking at which patients are at highest risk and the timeline for development of lymphdemea. This decade-long study aimed to identify lymphedema predictors and develop an algorithm estimating both risk and onset.

Methods: All patients undergoing axillary lymph node dissection (ALND) at Yale Cancer Center (YCC) between 2013–2024 were included. Demographic and clinical variables were collected, including age, BMI, race, ethnicity, chemotherapy, radiation, and comorbidities. Two multivariate regression models were developed to assess risk factors for lymphedema development and predict time to lymphedema diagnosis.

Results: Among 15,666 ALND cases, 2,345 patients (14.9%) developed lymphedema, with an average onset of 20.5 months post-surgery. Independent risk factors included BMI >30 (OR 1.385, 95% CI 1.255–1.528, p<0.0001), chemotherapy (OR 2.445, 95% CI 2.189–2.734, p<0.0001), diabetes (OR 1.168, 95% CI 1.040–1.312, p=0.0085), Black/African American race (OR 1.443, 95% CI 1.248–1.666, p<0.0001), and radiation (OR 1.960, 95% CI 1.777–2.162, p<0.0001). Radiation (β=-4.496, 95% CI -6.376 to -2.617, p<0.0001), Black/African American race (β=-4.159, 95% CI -6.876 to -1.442, p=0.027) and Asian race (β=-6.796, 95% CI -12.76 to -0.8300, p=0.0256) were associated with earlier onset, while preexisting diabetes was linked to delayed presentation (β=2.813, 95% CI 0.6189 to 5.008, p=0.0120). The model demonstrated adequate calibration (Hosmer-Lemeshow p=0.7985), with statistically significant discriminative ability (AUC = 0.6873, 95% CI: 0.6755–0.6990, p<0.0001).

Conclusion: This is the largest study to date to develop a clinically applicable prediction model for cancer-related lymphedema after axillary lymph node dissection (ALND). This model incorporates patient-specific demographics, clinical information and comorbidities. The Yale Cancer Center (YCC) lymphedema prediction model can be integrated into lymphedema care to proactively identify high-risk patients, estimate the timing of onset, and implement novel preventative strategies such as immediate lymphatic reconstruction. This predictive approach shifts the focus from late-stage management to prevention of this incurable condition, improving patient outcomes and long-term quality of life.

DISPARITIES IN BREAST CANCER-RELATED LYMPHEDEMA: A SYSTEMIC REVIEW OF INEQUITIES AND BARRIERS IN CARE

Mattia A., Hadzimustafic N., Rivero R., Oh S.J., Bach K., Brown S., Haykal S.

Introduction: Breast cancer-related lymphedema (BCRL) is an incurable, chronic, and often debilitating inflammatory condition caused by disruptions or trauma in lymphatic flow secondary to breast cancer (BC) treatment. Although BCRL incidence rates have been reported to be as high as 66% among breast cancer survivors (BCSs), causal associations between patient factors and BCRL development remain poorly understood. There remains a gap in the literature analyzing BCRL-specific care among females of racial and ethnic backgrounds and those living in rural geographic regions. Given the already cumbersome and challenging life-long management required for BCRL, vulnerable patients may face additional challenges and burdens.

Methods: The study protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO registration no. CRD42024597105). A search of PubMed/MEDLINE, Embase, Scopus, and Web of Science following the PRISMA guidelines was conducted from January 1, 1990, through October 3, 2024. Mixed-methods, qualitative, cross-sectional, multiple-case, longitudinal, and randomized controlled trials that reported disparities and barriers surrounding BCRL care were included. Review articles, editorials, commentaries, abstracts, poster papers, translation or validation of patient-reported outcome measures, and non-English articles were excluded.

Results: The search yielded 1059 articles, and 39 met inclusion criteria. Themes identified included the following: racial and ethnic disparities; increased risk with younger age, low education level, low income, rural geographic location, and presence of medical comorbidities; inadequate provider and patient knowledge; low patient education; burden and challenges with lifelong self-management; and barriers in receipt of healthcare provider diagnosis or adequate BCRL management. Subthemes included cumulative cost burden, psychosocial barriers, and the role of patient self-efficacy.

Conclusion: Younger non-Caucasian females, residence in rural regions, and those with low income or education levels appeared to be at greatest risk for self-reported (rather than physician-diagnosed) BCRL. Patients of diverse racial and ethnic backgrounds and low socioeconomic status were at increased risk for inadequate self-care practice education and breast cancer survivorship support. Active prevention with multidisciplinary interventions is imperative to lower BCRL rates, empower breast cancer survivors, and strengthen self-efficacy.

SELF-PERCEIVED BARRIERS TO HEALTHCARE EXPERIENCED BY PATIENTS WITH GASTROINTESTINAL CANCERS

Butensky, S.D., Godfrey, E., Kim, J., Kerekes, D., Su, D.G., Gamroudi, D., Kunstman, J., Olino, K., Billingsley, K.G., Turaga, K., Ahuja, N., Johnson, C.H., & Khan, S.A.

Introduction: Gastrointestinal cancer (GIC) treatment is complex, situating cancer patients at increased vulnerability in multiple facets of healthcare. We hypothesized that a diagnosis of GIC was associated with delays in care and affordability of treatment.

Methods: Prospectively collected data from The All of Us database was queried for GIC patients who completed the Healthcare Access and Utilization (HAU) survey. This cohort was separated by those who answered the survey less than 1 year after their diagnosis and those who answered more than 1 year after their diagnosis. These cohorts were propensity-matched based on age, race, sex, deprivation index, income, insurance, employment, and Charlson Deyo comorbidities. Regression was used to analyze the relationship between diagnosis to survey response time and survey scores.

Results: A total of 9,975 patients were included: 1,804 answered the survey less than 1 year after their cancer diagnosis, and 8,171 answered more than 1 year. Patients were most commonly white (88.5%), female (57.3%), non-Hispanic (99.0%), employed (40.8%), and earning $50,000-100,000 (30.5%). Colon cancer was most represented (75%), followed by anus (12%), rectum (6.2%), stomach (3.2%), and pancreas (0.9%) cancers. The median time between cancer diagnosis and survey response was 3.5 years (IQR 1.5-6.7 years). GIC patients surveyed before 1 year after diagnosis were more likely to have trouble affording healthcare compared to those surveyed after 1 year, including mental health counseling (OR 3.15, [95% CI: 2.13-4.78]), emergency care (OR 2.10, [95% CI: 1.32-3.45]), and prescription medications (OR 1.83, [95% CI: 1.33-2.62]). Patients surveyed before 1 year were more likely to experience delays in care due to inability to get time off work (OR 4.57, [95% CI: 2.93-7.46]), nervousness (OR 2.48, [95% CI: 1.85-3.37]), and childcare (OR 10.89, [95% CI: 3.23-67.9]). Lower income was associated with increased delays in care and decreased affordability. Income < $50,000 (vs. > $50,000) was associated with a lower likelihood of not affording emergency care (OR 0.24, [95% CI: 0.15-0.36]) and mental health counseling (OR 0.20, 95% CI: 0.15-0.28]).

Conclusion: Newly diagnosed gastrointestinal cancer patients perceive financial barriers to emergency healthcare, mental health counseling and prescription medications, and work and childcare lead to delays in cancer treatment. Societal and medical reforms following a cancer diagnosis are warranted.

EVALUATION OF SOCIAL SUPPORT, DISCRIMINATION, AND PERCEIVED HEALTH IN PATIENTS WITH GASTROINTESTINAL TRACT CANCERS

Butensky, S.D., Kim, J., Godfrey, E., Su, D.G., Kerekes, D., Ahuja, N., Johnson, C.H., and Khan, S.A.

Introduction: Health-related social conditions affect cancer outcomes. Gastrointestinal cancers (GIC) comprise a large proportion of cancers diagnosed in the United States. We hypothesized that a diagnosis of GIC negatively impacts Social Determinants of Health (SDOH) and perceived health (PH).

Methods: Prospectively collected data from The All of Us database was queried for GIC patients who completed SDOH and PH surveys. Healthy, non-cancer (NC) participants were matched to GIC based on age, race, sex, deprivation index, and Charlson Deyo comorbidities using Propensity Score Matching. Regression was used to analyze the relationship between cancer status and survey scores.

Results: A total of 231,033 patients met the criteria: 14,032 GIC and 217,001 NC. The majority of patients were white (69%%), female (59.2%), and non-Hispanic (97.2%). Colorectal cancer was most represented (81%), followed by anus (12%), stomach (3%), and pancreatic (1%) cancers. The median time between cancer diagnosis and survey response was 3.4 years (IQR 1.4-6.5 years). With respect to SDOH, GIC patients perceived more social support (β 0.07 [95% CI: 0.04, 0.10]), more neighborhood positivity (β 0.07 [95% CI: 0.05, 0.10]) and less healthcare discrimination (β -0.03 [95% CI: -0.06, -0.01]) (Table 1, NC is reference). GIC surveyed < 1 year after their diagnosis scored higher on social support than those surveyed > 1 year (β 0.13 [95% CI: 0.05, 0.21]). For PH, GIC were 15% more likely to report better mental health and 33% more likely to report better quality of life (QOL). Those diagnosed < 1 year before their survey had no difference in perceived physical and general health compared to NC, although their QOL (OR 1.3 [95% CI: 1.2-1.4]) and mental health (OR 1.1[95% CI: 1.0-1.2]) were similar to those surveyed > 1 year after the diagnosis. Chemotherapy-treated GIC patients reported better PH in all four domains, including QOL (OR 1.3, [95% CI: 1.2-1.5]) and mental health (OR 1.2, [95% CI: 1.1-1.4]).

Conclusion: Findings of this survey study reveal that a GI cancer diagnosis has a favorable impact on SDOH and PH - GIC feel more supported, less discriminated, and perceive better health compared to NC, and time of cancer diagnosis and chemotherapy impact outcomes. A concerted societal effort is required to improve health related social conditions for individuals with and without cancer.

ASSOCIATION BETWEEN CLOSE MARGIN STATUS AND SURVIVAL IN THE MODERN SYSTEMIC TREATMENT ERA FOR PANCREATIC DUCTAL ADENOCARCINOMA

Raymond-King L., Raymond-King C., Brown L., Feng W., Aravind P., Lacy J., Kunstman J.W.

Introduction: Pancreatic adenocarcinoma (PDAC) is ideally treated with surgery and systemic therapy. Historically, a resection margin of ≤1 mm was an important negative prognostic factor, with survivorship mirroring patients with a microscopically-positive margin. These initial reports predate the current era of multiagent systemic therapy regimens. The objective of this study was to evaluate the impact of close margin status and related clinicopathologic variables on survivorship in patients undergoing curative-intent resection for PDAC in the modern era.

Methods: We performed a retrospective analysis of patients undergoing resection for PDAC between 4/2015 and 4/2024 at a high-volume tertiary care hospital. The primary objective was to evaluate the impact of margin distance including a resection margin of >1 mm (R0), margin of ≤1 mm (R0close), or involved margin (R1) on overall survival (OS). Secondary objectives included assessing the relative impact of other clinicopathologic variables on survival. Unadjusted OS was determined via the Kaplan-Meier method and compared using a log rank test, while the relative contribution of individual variables was analyzed using a Cox proportional hazard model.

Results: We included 258 patients in this analysis; 217 (84.1%) underwent pancreaticoduodenectomy. The mean follow-up time was 36.8±26.0 months. R0 occurred in 163 patients (63.2%), R0close in 75 patients (29.1%), and R1 in 20 patients (7.8%). During the study period, median OS was 49.2 months (IQR=[21.5,not reached (NR)]); 57.1 months (IQR=[23.2,NR]) for R0, 37.2 months (IQR=[21.7,NR]) for R0close, and 21.4 months (IQR=14.4,NR]) for R1 (p=0.06). In those who underwent neoadjuvant therapy, the median OS was 48.6 months (IQR=[22.8,NR]); 55.5 months (IQR=[24.6,NR]) for R0, 37.7 months (IQR=[27.1, 58.5]) for R0close, and 21.4 months (IQR=[14.4,NR]) for R1 (p=0.35). The unadjusted Cox proportional hazard model did not show a significant difference between R0 and R0close (R0close HR = 1.33, 95%CI= (0.91,1.96)), but showed a significant difference between R0 and R1 (HR=1.94, 95%CI= (1.05,3.57)). Covariates negatively associated with survival included T3/T4 tumor size (HR=2.66, 95%CI= (1.35,5.23)) and N2 nodal status (HR=1.74, 95%CI= (1.03,2.94)).

Conclusion: 29.1% of patients had microscopically-negative resection margins of ≤1 mm. Survival linearly decreased among patients with R0, R0close, and R1 status, but there was no significant difference between R0 and R0close margins among all patients and among only those who received neoadjuvant chemotherapy. Covariates that were statistically associated with survival included tumor size (T3/T4) and nodal status (N2), indicating their increased relative significance compared to other predictors of mortality such as perineural or lymphovascular invasion and R0close status.

IMPACT OF NEOADJUVANT CHEMOTHERAPY ON OPERATIVE OUTCOMES FOLLOWING PANCREATICODUODENECTOMY FOR PANCREATIC ADENOCARCINOMA

Brown L, Raymond-King L, Fortoul M, Feng W, Abou Azar S, Khan S, Billingsley K, Lacy J, Salem R, Kunstman J

Introduction: Neoadjuvant chemotherapy (NAC) followed by surgery is an accepted curative approach to pancreatic ductal adenocarcinoma (PDAC), but its impact on surgical morbidity is unclear. Patients undergoing pancreaticoduodenectomy (PD) via a NAC or surgery-first (SF) approach were matched for surgical risk and outcomes were compared.

Methods: A prospectively collected dataset of patients undergoing PD for PDAC at a high-volume institution between April, 2012 and March, 2020 was queried. Receipt of ≥2 cycles of chemotherapy defined the NAC cohort. Morbidity risk was quantified by “Serious Complication” risk using the ACS-NSQIP Surgical Risk Calculator and the Fistula Risk Score quantified clinically-relevant pancreatic fistula risk (CR-PF). Patients were stratified by NAC or SF and propensity matched 1:1 by both risk metrics. Primary outcomes were 90-day major morbidity (Clavien-Dindo Grade ≥3) and CR-PF rate. Secondary outcomes included overall survival (OS), tumor pathology, and perioperative outcomes. Categorical and continuous variables were assessed via Chi-squared and two-tailed t-tests, respectively; survival analysis was via the Kaplan-Meier method.

Results: 259 patients underwent curative-intent PD and were assessed for matching; of these,106 patients comprised the study cohort. The mean ACS-NSQIP risk was 27.5±3.8% and 28.0±4.8% in the NAC and SF cohorts, respectively (p=0.61). Of the NAC patients, the median number of preoperative cycles was 8 (IQR 6-9); 88.7% received FOLFIRNOX. 22.6% of NAC patients required non-index biliary procedures prior to surgery compared to 1.9% of SF patients (p<0.01). There was no difference between the matched NAC and SF cohorts in major morbidity (17.0% vs 15.1%, p=1.0), CR-PF incidence (0% vs 5.7%, p=0.07), or operative mortality (1.9%, both). Index length of stay (5.9±3.9d [NAC] vs 5.8±3.1d [SF], p=0.80) and readmission rates (15.1% [NAC] vs 28.3% [SF], p=0.12) were similar. Operative blood loss was higher in NAC compared to SF patients (544.7±576.7 mL vs 305.1±190.4 mL; p=0.01).
Contrasting SF to NAC patients, 13.2% compared to 3.8% had a positive (R1) margin (p=0.16) whereas 79.3% compared to 49.1% had regional (N1/2) disease (p=0.01), respectively. Median OS was 39.4 months following NAC versus 25.7 compared to SF (p=0.34).

Conclusion: Patients undergoing PD for PDAC following NAC compared to SF when matched by surgical risk experienced increased operative blood loss but had no detrimental effect on overall postoperative major morbidity, CR-PF rate, or related operative outcomes.

GENDER REPRESENTATION OF ACCEPTED ABSTRACTS AT THE SOCIETY OF THORACIC SURGEONS' ANNUAL MEETING ACHIEVING SUCCESSFUL MANUSCRIPT PUBLICATION

Acuna Higaki A., Bilgili A., Ramdeen S., Waldron C., Asmelash S., Sharaf O., Papageorge M., Woodard G.A., Ailawadi G., Romano J.C., Jacobs J.P., Lee M.E.

Introduction: The Society of Thoracic Surgeons (STS) annual meetings are an important component of academic productivity and research dissemination. Although the success rate of accepted abstracts ultimately reaching publication in a peer-reviewed journal was found to be relatively high (>75%) in a previous study, understanding whether gender may be a factor for the eventual fates of these STS abstracts is an important aspect to consider when reflecting on gender disparity and academic promotion within cardiothoracic surgery.

Methods: The STS annual meeting abstract books were searched online from 2015 to 2019 for presented abstracts. Subsequent PubMed and Google searches were performed to identify corresponding peer-reviewed journal publications. Programming was then used to query PubMed databases for full author first and last names. Validated software was used to classify the gender of abstracts' and manuscripts' first and last authors.

Results: Among 1451 total presented abstracts 21.2% (n=308) had a corresponding women first authors and 11.9% (n=172) had women senior authors. From 2015 to 2019, the number of presentations by women authors has fluctuated, with the 2016 meeting with the greatest number of female presenters (29.5% [n=91]) and 2018 with the fewest (13.3% [n=41]). When analyzing the presented abstracts by women first authors, the majority of categories of abstracts presented were oral presentations (50.6% [156/308]), measured clinical outcomes (89.9% [n=277/308]), and retrospective (76.6% [n=236/308]). When evaluating by publication rates for accepted abstracts, there were no differences comparing abstracts presented by women versus men first authors (71.8% [n=221] versus 76.6% [n=876], p =0.09) or women versus men senior authors (75.6% [n=130] versus 75.6% [n=967], p =0.99). The majority of abstracts presented by women first authors were published in one North American peer-reviewed cardiothoracic surgery journal (72.9% [n=161/221]) with a median time from presentation to publication of 313 days [IQR:222-403].

Conclusion: The initial acceptance of STS abstracts correlates with a similar previously reported gender breakdown of women composing the minority of acceptance as either first or senior authors. However, no gender disparity was identified when comparing accepted STS abstracts successfully published in a peer-reviewed journal. The results of this study indicate that perhaps earlier intervention in the preliminary stages of academic productivity processes (i.e., abstract submission, faculty retention, etc.) may require similar improvements in order to reflect the progress in publication rates in peer-reviewed journals after abstract acceptance.

ARE NEIGHBORHOOD-LEVEL INDICES ASSOCIATED WITH PATIENT-LEVEL SOCIOECOLOGICAL RISK BEFORE ELECTIVE, MAJOR SURGERY?

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Introduction: Neighborhood-level socioecological indices are frequently used as a proxy for a patient's socioecological risk. However, it is unknown whether these measures are an appropriate surrogate for an individual's true risk. This study aimed to evaluate the association of neighborhood-level indices with patient-level social risks.

Methods: This was a prospective study of adult patients undergoing elective major surgery within a statewide health system from July 2023 to September 2024. Patients were recruited from thoracic surgery, surgical oncology, and colorectal surgery services. Two neighborhood-level indices based on the 2020 United States Census data were employed: the Area Deprivation Index (ADI) and the Social Vulnerability Index (SVI). The SEDOH-88 survey, a comprehensive, patient-reported socioecological survey, was used as the patient-level measure. The survey was conducted with patients before surgery via structured, researcher-administered 45-minute interviews. Higher scores on any of the three measures represent higher socioecological risk. The relationship between ADI and SVI with SEDOH-88 was assessed using the area under the receiver operating characteristic curve (AUC), logistic regression and Spearman's rank correlation coefficient.

Results: Of 345 patients contacted, 192 (55.7%) patients agreed to participate, with a median age of 65.1 [IQR, 52.6-72.9] (55.4% (n=107) female, 8.3% (n=16) non-White, and 7.8% (n=16) Hispanic). Twenty-four percent (n=47) of patients underwent surgery on the thoracic surgery service, 16.1% (n=31) on the surgical oncology service, and 59.1% (n=114) on the colorectal surgery service. Overall, the 30-day complication rate was 12.5%. The median ADI score was 30 (IQR, 20-44, range: 1-99), the median SVI score was 0.29 (IQR, 0.13-0.54, range 0.003-0.98), and the median SEDOH-88 score was 5 (IQR, 4-8, range: 0-31). ADI and SVI had poor discrimination with the SEDOH-88 score, with an AUC of 0.636 and 0.664, respectively. On multivariable logistic regression, high SEDOH-88 was associated with higher deprivation on SVI (OR, 5.34, 95% CI, 1.36-21.57, p=0.017), whereas SEDOH-88 was not associated with neighborhood deprivation on ADI (OR, 1.01, 95% CI, 0.99-1.03, p=0.201). Neither ADI (rho=0.18, p=0.012) nor SVI (rho=0.19, p=0.007) correlated well with SEDOH-88.

Conclusion: There was limited agreement between neighborhood-level indices and a patient-level socioecological risk assessment for patients undergoing major surgery. SVI is more granular than ADI and had a stronger association with SEDOH-88. The reliance on neighborhood-level socioecological risk data is likely inadequate for studying the effect of individual risk on surgical outcomes.

TOWARDS AN ARTIFICIAL INTELLIGENCE NURSE: COMPARING CUSTOM LLMS AGAINST GPT-4O FOR POST-OPERATIVE RHINOPLASTY CARE

Munshi M, Barbarite E, Derakhshan A, Gadkaree S, Lee C, Lee YH, Mohan S

Introduction: Recent advancements in large language models (LLMs) have shown potential in patient-centered applications, including post-operative care. While prior studies suggested custom “fine-tuned” models outperform public models like ChatGPT, rapid AI improvements raise questions about this assumption. We aimed to test whether fine-tuned models still outperform base models like GPT-4o.

Methods: A custom-trained LLM or “AI nurse”, was developed for post-operative rhinoplasty care, fine-tuned using few-shot learning with ~100 common questions answered by a facial plastic surgeon. The model was compared to GPT-4o, which was prompted as usual. Five facial plastic surgeons from various institutions evaluated both models using a 5-point Likert scale across five domains—medical accuracy, conciseness, overall quality, professionalism, and empathy—and a modified Patient Education Materials Assessment Tool (PEMAT-P). Evaluators were blinded to the model being assessed.

Results: GPT-4o significantly outperformed the custom model in overall quality (mean difference = 1.00, $p = 0.0018$), professionalism (mean difference = 0.84, $p = 0.0024$), and empathy (median difference = 1.76, $p < 0.0001$). There was no significant difference in medical accuracy or conciseness between the models. The modified PEMAT-P also favored GPT-4o for understandability (93.3% vs 73.6%, $p < 0.0001$) and actionability (90.0% vs 70.0%, $p = 0.0002$).

Conclusion: Simple prompting of GPT-4o can outperform custom-trained models. As machine learning tools are incorporated into the clinical setting, the benefit and need for customization will need to be carefully re-evaluated. Future research will involve testing GPT-4o with patients and exploring voice-to-voice technology to better mimic traditional care modalities.

PATIENT-REPORTED BARRIERS TO COMPLETING IN-PERSON PELVIC FLOOR PHYSICAL THERAPY REFERRALS

Aloul ZS., Schultz KS., Linhares SM., Leeds IL., Pantel HJ., Murthy SS., Reddy VB., Mongiu AK.

Introduction: Pelvic floor dysfunction is a common and debilitating condition impacting over 28 million Americans. While pelvic floor physical therapy (PFPT) is effective in addressing this condition, many patients referred for PFPT either do not attend or fail to complete the recommended number of sessions. This study aims to identify the patient-reported barriers to completing in-person PFPT and evaluate their willingness to use a mobile, video-based, or hybrid platform as an alternative.

Methods: This was a retrospective study of adult patients with pelvic floor dysfunction referred to a pelvic floor therapist across a statewide academic healthcare system from January 2022 to October 2024. Patients completed a structured phone survey on their perceived barriers to care and willingness to use a mobile, video-based platform to complete PFPT. Patients were excluded if they could not complete the study due to language difficulties, intellectual impairment, or visual/hearing deficits.

Results: Of 200 patients contacted, 50 (25% response rate) agreed to participate. The majority (94%) of respondents were female, with 10% identifying as Black or African American and 4% as Hispanic. The three most common referral reasons were urinary incontinence (33%), fecal incontinence (17%), and pelvic pain (13%). Referral sources included gynecologists (24%), urologists (20%), and colorectal/general surgeons (8%). The average time between referral and the first scheduled appointment was 10 weeks, and the average time interval between the first and last PFPT sessions was 15 weeks. Among patients who identified barriers to attending PFPT sessions, the most common barrier was sessions being scheduled too far in the future (23%), followed by the time commitment (16%) and the travel distance to sessions (14.9%). The average commute time was 26 minutes. Fourteen percent of participants (n=7) reported they would attend “many more sessions” if the sessions were mobile video-based, while 42% (n=21) would attend “a few more sessions.” Forty-eight percent of participants (n=24) reported no barriers to using a mobile video-based platform, while 32% (n=16) preferred in-person sessions. Preferences for session formats included in-person sessions (62%) and a hybrid or mobile video-based platform (32%), and 6% had no preference.

Conclusion: This study identifies significant patient-reported barriers to completing in-person PFPT, including the long appointment wait times, the time commitment, and the distance to travel to sessions. Many patients preferred mobile video-based or hybrid PFPT sessions, suggesting that mobile platforms could improve access and adherence to physical therapy for patients with pelvic floor dysfunction.

A SYSTEMATIC REVIEW OF SURGICAL CARE FOR PERSONS EXPERIENCING HOMELESSNESS WITH CANCER

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Introduction: Over 3.5 million people experience homelessness (PEH) in the US annually and cancer related deaths are twice as high in PEH compared to the general population. Oncologic management of PEH is influenced by social determinants of health (SDOH) including lack of health insurance, housing, and unreliable transportation as cancer care requires multimodal diagnostic workups and therapies by a multidisciplinary team. To improve cancer related mortality, SDOH and their influence on surgical cancer outcomes should be a focus for surgeons. However, there is a paucity of literature examining surgical cancer care in PEH. The objective of this review is to examine disparities in surgical access, treatment, and cancer outcomes for PEH.

Methods: A systematic review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. An initial search used terms of homelessness, cancer, and surgery. References were identified in databases including OVID MEDLINE, OVID Embase, Web of Science-Core Collection, Scopus, Healthcare Administration Database, Cochrane CENTRAL, as well as Google Scholar and grey literature. Papers were selected in 3 phases: two reviewers (HA/WF) independently screened abstracts, and assessed full text articles for eligibility, and discrepancies were reviewed by SSM

Results: A total of 1073 papers were generated, and 26 papers met inclusion criteria -13 case studies, 9 cohort studies, 2 op eds and 2 reviews. Articles assessed from 22 to 2 million patients and covered a range of cancers including lung, colorectal, breast, and melanoma. Significantly more PEH presented with advanced cancers compared to the general population, and few received surgical treatment. Moreover, studies suggested PEH have inconsistent primary medical care, which may play a role in delayed diagnoses, advanced stage presentation, reduced access to surgeons, and treatments at non-specialist sites. Many PEH patients were ultimately lost to postoperative follow-up and long-term cancer surveillance.

Conclusion: Although cancer-related deaths are higher in PEH compared to the general population, there are few studies examining challenges faced by PEH when receiving surgical cancer care. This literature review provides insight into major barriers, including reduced access to surgeons, delays in diagnosis, and treatment at non specialist sites. Further work focused on solutions is warranted, such as developing routine screening programs and pathways for PEH cancer patients to readily access surgical care.

A COLONOSCOPY TRAINING PROGRAM FOR LOW- AND MIDDLE- INCOME COUNTRIES - A PILOT RANDOMIZED CONTROL TRIAL IN NIGERIA

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Introduction: Colorectal cancer is the third most common cause of cancer deaths globally. Increasing the number of healthcare personnel trained in colonoscopy in low- and middle-income countries (LMIC), such as Nigeria, is critical. Simulation-based training can play a key role in creating competent providers. We hypothesize that a locally designed and sustainably produced low-fidelity (LF) colonoscopy simulator is as effective as a high-fidelity (HF) simulator in acquiring the requisite skills required to perform a colonoscopy and can be incorporated into the training of medical practitioners with varying experience which can lead to an increase in local endoscopic capacity.

Methods: This randomized controlled trial consisted of a nine-week online lecture series and a four-day in-person colonoscopy training workshop. The participants included surgeons, residents, and gastroenterologists with varying levels of experience. Their knowledge was evaluated through a pre- and post-course exam, while a self-designed tool assessed their confidence levels before and after training. Participants were randomly assigned in a 1:1 ratio to use either a HF or LF simulator. Their performance was evaluated at baseline, after training on their assigned model, and on patients using the Mayo Colonoscopy Skills Assessment Tool (MCSAT) and the Global Assessment of Gastrointestinal Endoscopic Skills (GAGES) tool. The primary outcome measured was the difference in scores between the two groups following the training. Secondary outcomes included changes in online exam scores and the participants' confidence levels.

Results: There were 19 participants enrolled in the program with one dropout. There was no statistically significant difference between the two groups in the performance scores when a colonoscopy was done on patients after training on their assigned models. For the LF model, there was a statistically significant improvement in the GAGES overall assessment score from a median of 9(9.0-17.5) to 20(15-20.0) $p=0.027$ and a trend towards improvement in specific skills. For the HF model, there was no statistically significant difference in the performance measures on either tool after training. There was a significant increase in the pre and post-test scores of the online lecture series from a mean of 27.5(±5.5) to 34.5(±4.0) $p<0.001$. The training program led to an improvement in the confidence of the participants in performing colonoscopies with an average doubling of scores ($p=0.001$).

Conclusion: This trial demonstrated that training on HF versus LF model results in similar test scores and can improve the skills needed to perform a colonoscopy. This inexpensive model can be used to facilitate colonoscopy training in LMICs.

GENDER AND INCOME-BASED VARIATIONS IN GLOBAL CANCER BURDEN

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Introduction: Over 35 million new cancer cases are predicted in 2050, a 77% increase from estimated cases in 2022. Despite this rising burden, there is a paucity of literature on global incidence and mortality trends affecting the female population. The aim of this study is to analyze variations in global cancer burden based on gender and income.

Methods: Data was obtained via the GLOBOCAN 2022 report. Countries were divided by World Bank (WB) income classification groups: low-income countries (LIC), lower middle-income countries (LMIC), upper middle-income countries (UMIC), and high-income countries (HIC). We analyzed trends (absolute numbers and proportional changes) in cancer incidence and mortality (overall and gender-specific burden) by WB income level for males and females from 2022-2050.

Results: In 2022, there were an estimated 20.4 million new cancer cases and 9.74 million cancer-related deaths (CRDs) globally, with UMIC (7.81 and 4.11 million) and HIC (7.78 and 2.83 million) accounting for the majority. Although males accounted for a larger proportion globally, females contributed more towards respective gender-specific global burden for incidence (LIC, LMIC & UMIC) and CRDs (LIC, LMIC and HIC). This female-dominant trend was more pronounced for LIC and LMIC.

The global cancer burden is predicted to increase in both genders and across all income to a combined 35.3 million new cancer cases (76.5%) and 18.5 million CRDs (89.9%) by 2050. However, proportional increases (absolute number) in incidence and CRDs are notably higher in LIC (151% & 155%) and LMIC (96.1% & 107%), when compared to UMIC (58.8% & 84.9%) and HIC (38.8% & 55.8%). Additionally, the proportional contribution to global cancer burden (incidence/CRDs) will increase in LIC (42.2 and 34.4%) and LMIC (11 & 9.27%), while decreased in UMIC (10.2 & 2.61%) and HIC (21.3 & 18.2%).

Gender-based analysis showed that, by 2050, males will have greater increases in incidence and mortality globally (84.5 & 93.4%) compared to females (68.7 & 85.4%). However, females will continue to contribute more towards rising gender-specific global cancer burden in LIC and LMIC while males will maintain predominance in UMIC and HIC.

Conclusion: The global cancer burden is predicted to rise drastically over the next few decades, with greater proportional increases for females in LIC/LMIC and contrasting decreases in UMIC/HIC. Future policy decisions should take these trends into account and allow for resource allocation to these vulnerable populations, such as females in lower income regions of the world.

RISK FACTORS FOR POSTOPERATIVE DELIRIUM AFTER ABDOMINAL AORTIC ANEURYSM REPAIR AMONG OLDER ADULTS

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Introduction: Postoperative delirium is a significant but underreported complication after aortic surgery in older adults. Abdominal aortic aneurysm (AAA) repair can impart significant physiological stress that may predispose to delirium. This study aims to characterize risk factors for delirium after AAA repair in older adults using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database.

Methods: The ACS-NSQIP database was queried for intact AAA repairs and linked to the Geriatric Surgery module and open and endovascular AAA repair targeted modules. The primary outcome was postoperative delirium, determined by a standardized chart-based assessment. Demographics, clinical characteristics, and postoperative outcomes were compared between patients with and without delirium. Backward stepwise logistic regression identified factors independently associated with delirium.

Results: There were 529 cases (75% endovascular) with geriatric and AAA repair details available. Delirium incidence was 9.5% and more common following open repair compared to endovascular repair (23.8% vs 4.8%; $p<0.001$). Patients with delirium were more likely to be older (77 vs 75 years; $p=0.022$), have lower BMI (26.7 vs 28.5; $p=0.008$), and be at increased bleeding risk preoperatively (24% vs 12%; $p=0.028$), but otherwise did not differ in baseline medical comorbidities. Geriatric assessments demonstrated that rates of preoperative cognitive impairment (9.6%), mobility aid use (19%), falls within the past year (11%), and surrogate-signed consents (3.1%) also did not differ between patients with and without delirium. However, patients with delirium were more likely to have been living alone preoperatively (33% vs 17%; $p=0.028$). Postoperatively, patients with delirium had significantly more complications and longer hospital lengths of stay. At discharge, 21% of all patients were functionally dependent, compared to 1.5% preoperatively. Patients who had delirium were significantly more likely to be functionally dependent (49% vs 19%) and require mobility aids (65% vs 21%) at discharge compared to patients without delirium ($p<0.001$). Across the entire sample, 30-day mortality was low (1.5%), but patients who suffered from delirium had a significantly higher mortality rate (18% vs 0.4%; $p<0.001$). On multivariable analysis, older age, increased bleeding risk, open AAA repair, and paravisceral (i.e., juxtarenal, pararenal, suprarenal, type IV thoracoabdominal) aneurysm extent were independently associated with delirium.

Conclusion: Among older adults undergoing AAA repair, operative factors were more strongly associated with delirium than patient characteristics. Delirium prevention bundles and close monitoring should be prioritized in the perioperative care of older adults at high risk, such as those undergoing open AAA repair.

THE INCIDENCE AND IMPACT OF DISCORDANCE IN INTERPRETATION OF CROSS-SECTIONAL IMAGING BETWEEN VASCULAR SPECIALISTS AND RADIOLOGISTS IN PATIENTS WITH DEEP VENOUS STENOSIS

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Introduction: Intravascular ultrasound (IVUS) is the preferred method for diagnosing iliocaval deep venous stenosis (DVS). Preoperative cross-sectional imaging (CSI) is used to screen for DVS in selected patients but there is no current standardization of radiological measurement and reporting. Our hypothesis is that discordance in CSI interpretation between vascular specialists and radiologists could impact patient care and outcomes.

Methods: A retrospective analysis of patients who underwent deep venous stenting after CSI for chronic venous symptoms was performed. Vascular specialists reviewed all CSI scans for significant DVS (≥50%) and compared them to the official radiologist reports. Patients were divided into two groups based on the interpretation of CSI: discordant reading (DR) and concordant reading (CR). The DR group consisted of cases where the vascular specialists' interpretation differed from that of the radiologist, while the CR group included cases where there was agreement.

Results: Ninety-three patients underwent stenting for DVS with preoperative CSI and 27% had DR. There were more female patients in the CR group, with no other demographic differences. There were significantly more patients in the CR group with a history of anticoagulation use than patients with DR. There was no difference in presenting symptoms based on CEAP clinical classification between the two groups. MRI was the most used CSI modality (64.5%) with no difference between the groups. There was a significantly higher proportion of patients with common iliac vein (CIV) stenosis in the DR group compared to the CR group reaching up to 96% suggesting that the interpretation of significant CIV stenosis is the source of most discordances. IVUS revealed significant iliac vein stenosis in the majority of patients (96.8%) regardless of CSI. After a mean follow-up of 2.5 years, both groups had similar symptomatic relief (95% vs. 98%; p=0.5) and primary patency.

Conclusion: This study reveals significant discordance between vascular specialists and radiologists in the interpretation of CSI of DVS related mostly to measurement of the CIV. Even though patients had excellent outcomes in both groups, standardization of measurement and reporting of DVS on CSI could improve patient selection for therapy.

ANTITHROMBOTIC THERAPY IN PATIENTS WITH ISOLATED PERIPHERAL ARTERIAL DISEASE UNDERGOING PERIPHERAL VASCULAR INTERVENTIONS

Shreef Said, Dana Alameddine, Uwe Fischer, Hannah Zwibelman, Loay Kabbani, Vikram S. Kashyap, Britt Tonnessen, Jonathan Cardella, Raul J Guzman, Cassius Iyad Ochoa Chaar

Introduction: Comorbidities and procedural history can significantly influence the choice of antithrombotic therapy in patients undergoing peripheral vascular interventions (PVI) for peripheral arterial disease (PAD). The landscape of antithrombotic therapy is growing in complexity with paucity of trials dedicated to patients with PAD. This study assesses antithrombotic regimens in patients presenting with isolated PAD, without other comorbidities or procedural history that could affect antithrombotic management.

Methods: The Vascular Quality Initiative (VQI) PVI database was reviewed. Only patients with isolated PAD without history of cardiovascular or cerebrovascular disease, or other indications for antithrombotic therapy were included. Patients presenting with acute limb ischemia or chronic anticoagulation preoperatively were excluded. The characteristics and outcomes of patients discharged on factor Xa inhibitor plus single antiplatelet therapy (FXaI+SAPT) were compared to patients discharged on dual antiplatelet therapy (DAPT).

Results: A total of 191,421 patients underwent PVI and 60% of patients were excluded because of competing indications for antithrombotic therapy. Isolated PAD constituted only 40% of the sample (N=75,334) and exhibited extensive variations in the medications prescribed at discharge, totaling 40 unique combinations. The most common class combinations were DAPT (Aspirin+P2Y12i) was used in 59% of patients, followed by SAPT (Aspirin or P2Y12i) in 30%, FXaI+SAPT in 2.6%, and 5.5% were discharged without antithrombotic medication. Patients received FXaI+SAPT (N=1,914) were more likely to be younger (65 vs. 67; P<0.001) and African American (20% vs. 18%; P<0.001) compared to patients received DAPT (N=43,807) but were less likely to have diabetes (40% vs. 46%; P<0.001) and chronic kidney disease (63% vs. 70%; P<0.001). Patients discharged on FXaI+SAPT were more likely to be treated for chronic limb-threatening ischemia compared to patients discharged on DAPT (71% vs. 52%; P<0.001). After 3:1 propensity matching, there were 5,890 patients included in the analysis with no differences in baseline characteristics.
Patients received FXaI+SAPT had higher rates of thrombosis and embolism postoperatively and were less likely to be discharged home. Patients received FXaI+SAPT had higher rates of long-term reintervention and major amputation (Table). Kaplan-Meier curves showed a significantly lower overall survival, freedom from amputation, and MALE-free survival for patients receiving FXaI+SAPT compared to patients receiving DAPT upon discharge.

Conclusion: Most patients with PAD undergoing PVI have competing indications for antithrombotic therapy. There is a wide variation in the antithrombotic regimens of patients with isolated PAD. DAPT seemed to be associated with better long-term outcomes compared to FXaI+SAPT for patients with isolated PAD undergoing PVI.

CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH AND WITHOUT BLEEDING AFTER LOWER EXTREMITY REVASCULARIZATION IN ADVANCED PERIPHERAL ARTERIAL DISEASE

Addiskidan Hundito, Nicholas Wells, McKenzie Tuttle, Dana Alameddine, Joshua Huttler, Martin Slade, David Strosberg, Alfred Lee, Raul J Guzman, Cassius Iyad Ochoa Chaar

Introduction: As novel medications are used in various combinations to prevent thrombosis, few studies have focused on bleeding events after lower extremity revascularization (LER) in patients with peripheral artery disease (PAD). Moreover, the impact of bleeding events on long-term outcomes and the prescription of antithrombotic therapy is not well reported. This study examines the incidence of bleeding events after LER and their significance in patients with advanced PAD.

Methods: A retrospective review of patients undergoing LER for PAD in a tertiary care center was performed. Bleeding was classified into major and minor based on the International Society of Thrombosis definitions and captured outside the 30-day perioperative period of LER. Characteristics and outcomes of patients who experienced bleeding events more than 30 days after initial LER were compared to patients who did not.

Results: A total of 1,932 patients underwent LER and 529 (27.4%) experienced a bleeding event (53% major, 47% minor) over 4.3 years. Patients who experienced a bleeding event were more likely to have hypertension (93% vs 89%, p = .005), coronary artery disease (58% vs 53% p = .047), chronic renal insufficiency (25% vs 16%, p < .001), end-stage renal disease (12% vs 6.8%, p < .001), a history of smoking (84% vs 79% p = .007), and be on dual antiplatelet therapy (DAPT) (31% vs 25%, p = 0.029) at baseline. Patients who experienced a bleeding event after 30 days were also more likely to have developed perioperative bleeding (7.6% vs 5.2% p = 0.049) after the first LER. On follow-up, patients with bleeding were more likely to have reinterventions (51% vs 43%, p = .002), major amputation (14% vs 7.1%, p < .001), myocardial infarction (33% vs 17%, p <0.001), stroke (9.5% vs 5.1%, p <0.001), and mortality (48% vs 38%, p < .001). The most common type of bleeding was gastrointestinal (47%) followed by surgical site unrelated to LER (13%), and intracranial. Blood transfusion was used in 48%. Moreover, 40% of patients with an initial bleeding episode had at least one recurrent bleeding episode with a mean of 2.9 bleeding episodes per patient. After the first bleeding episode, 15% of patients were discharged without any antithrombotic therapy and 13%, 16%, and 11% had discontinuation of ASA, P2Y12 inhibitors, and anticoagulation respectively.

Conclusion: Bleeding events are common after LER for advanced PAD and are associated with worse overall outcomes. Recurrent bleeding events are likely and significantly affect antithrombotic medication prescriptions.

THORACIC AORTA MEASUREMENT EXTRACTION FROM CT RADIOLOGY REPORTS USING INSTRUCTION TUNED LARGE LANGUAGE MODELS

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Introduction: Chest computed tomography (CT) plays a crucial role in diagnosing and monitoring thoracic aortic dilations and aneurysms. However, aortic measurements in radiology reports are often embedded in free text, limiting their accessibility. This study compares the performance of BERT-based and Llama models in extracting aortic measurements from radiology reports to create an institutional chest CT aortic measurement database.

Methods: A dataset of 363,424 chest CT narratives (2013–2023) was curated through an institutional search. A randomly selected subset of 2,010 narratives was manually annotated: 1,002 for training, 504 for validation, and 504 for testing. Aortic diameters were labeled at eight anatomical sites: annulus, sinus of Valsalva, sinotubular junction, mid-ascending, ascending proximal to the brachiocephalic artery, top of the arch, proximal descending, and mid-descending aorta. The macro-averaged F1 scores of zero-shot and few-shot Llama 3.1 instruct models were compared with those of fine-tuned BERT-based models and multiple instruction-tuned Llama instruct models. The optimal model was then used to extract aortic measurements from the complete radiology report cohort to construct an aortic measurement database. Model development was conducted in Python using PyTorch and the Hugging Face Transformers library. Analysis was performed on a HIPAA-compliant virtual machine hosted by Yale's Spinup service, equipped with an NVIDIA T4 GPU.

Results: The instruction-tuned Llama 3.1 model achieved the highest overall performance, with a macro F1 score of 0.992. Few-shot and zero-shot Llama 3.1 models obtained macro F1 scores of 0.838 and 0.663, respectively. Among BERT-based models, fine-tuned PubMedBERT performed best (macro F1 = 0.945). Using the instruction-tuned Llama 3.1 model, aortic measurements were identified in 49,387 of 356,690 radiology reports (13.85%), with a higher extraction rate in males than females (18.51% vs. 9.50%). The largest median diameters were observed at the mid-ascending aorta (39 mm, IQR 36–42) and the sinus of Valsalva (36 mm, IQR 32–40). Ascending aortic dilation of at least 40 mm was reported in 8.69% of patients (12,228/140,645), with 2.27% (3,193/140,645) having dilations of at least 45 mm, 0.66% (925/140,645) at least 50 mm, and 0.28% (393/140,645) at least 55 mm.

Conclusion: Instruction-tuned large language models can effectively extract aortic measurements with relatively few manual annotations. The developed framework is easily adaptable to other medical entities and unstructured text sources, facilitating AI/ML research by unlocking previously inaccessible clinical data.

IDENTIFYING POTENTIAL SURGICAL NEED AND EXAMINING ACCESS TO CARE AMONG SYRIAN REFUGEES LIVING IN LEBANON

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Introduction: Since 2011, the Syrian war has displaced more than 14 million people, 6.2 million of whom remain refugees today. Lebanon hosts more than 1.5 million displaced Syrians, the largest proportion per capita of any country, most of whom live in informal settlements scattered around the country. This national study aims to identify potential surgical needs among displaced Syrians in Lebanon and to assess access and barriers to surgical care.

Methods: A cross-sectional, cluster-sample survey (adapted from the SOSAS tool, version 3.0) was used in informal Syrian refugee settlements across Lebanon. Households were asked about deaths in the home over the previous year before individual respondents were asked about their personal health.

Results: A total of 2,936 respondents representing 1,468 households were surveyed. Over the 12 months preceding the study, 6.4% of households experienced a death, a rate of 32 deaths per 1,000 population. Common conditions reported in those who died that may indicate a surgical need included masses, injury, and acquired deformity. Respondents reported that 19.6% of household members who died in the prior 12 months received surgical care before their death. Individual respondents reported 4,192 potential surgical conditions including wounds (55.2%), deformities (35.8%), and masses (7.1%). Most respondents (86.2%) sought medical care for these conditions and surgery was recommended in 19.0% of cases. Of those conditions for which surgery was recommended, only 34.8% were treated with a surgical procedure. Respondents cited financial burden as the main barrier to surgical care. Many respondents reported continued impacts of these conditions on their lives including inability to work (20.8%), assistance with activities of daily living (7.1%), and feeling shame (5.8%).

Conclusion: The death rate of Syrian refugees surveyed is three times higher than the host population in Lebanon. Respondents reported various conditions that may benefit from surgical care including high numbers of wounds, masses, injuries, and deformities. Financial constraints remain a major barrier to obtaining surgical care for Syrian refugees in Lebanon. The unmet need for surgical care remains an important public health and social problem that impacts the health, ability to work, and care for oneself in this population.

COMPARATIVE OUTCOMES OF TOTAL VS. UNICOMPARTMENTAL KNEE ARTHROPLASTY: A NATIONAL ANALYSIS OF COMPLICATIONS AND REVISION RATES

Ajjawi I., Slevin J., Rubin L. E., Grauer J. N.

Introduction: Knee arthroplasty is a common procedure for treating end-stage osteoarthritis. While total knee arthroplasty (TKA) is the standard, unicompartmental knee arthroplasty (UKA) offers an alternative for patients with unicompartmental disease. However, concerns about UKA's durability relative to TKA persist. The current study compared 90-day complication rates and 5-year revision rates following UKA and TKA.

Methods: Using the M165Ortho 2010 and 2022 PearlDiver Mariner Database, patients who underwent TKA or UKA were identified, excluding those with neoplasm, infection, or trauma. A 1:4 matching algorithm was applied based on age, sex, and Elixhauser Comorbidity Index (ECI). Ninety-day adverse events were compared using multivariate analyses, and five-year revision rates were analyzed using Kaplan-Meier analysis.

Results: From 1,720,705 patients, 113,542 underwent UKA and 1,607,163 underwent TKA. After matching, 113,512 patients were in the UKA cohort and 454,048 in the TKA cohort.
UKA was associated with significantly lower odds of 90-day adverse outcomes compared to TKA, including AAE (OR 0.69), SAE (OR 0.68), and MAE (OR 0.67) ($p<0.001$ for each). Specific complications less common in UKA included wound dehiscence (OR 0.79), pneumonia (OR 0.78), surgical site infections (OR 0.68), DVT (OR 0.65), pulmonary embolism (OR 0.55), sepsis (OR 0.50), readmissions (OR 0.50), acute kidney injury (OR 0.47), cardiac events (OR 0.41), and transfusions (OR 0.20) ($p<0.001$ for each).
Contrary to questioned, the five-year revision rates were lower for UKA (2.4%) than for TKA (3.8%) ($p < 0.001$).

Conclusion: This large, nationally representative study evaluated patients undergoing UKA and compared them to patients undergoing TKA. After matching, 90-day complications were lower for UKA as expected for a smaller surgical intervention. Notable was the lower five-year revision rates for UKA, suggest it to be a durable procedure when appropriate candidates are selected.

OPIOID PRESCRIPTION PATTERNS FOLLOWING ZONE II FLEXOR TENDON REPAIRS: A NATIONAL DATABASE STUDY

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Introduction: The opioid epidemic continues to be a major public health concern, with postoperative opioid prescriptions contributing to side effects and long-term use / dependency. Given the evolving landscape of opioid prescription and use, the current study sought to investigate opioid prescribing patterns following zone II flexor tendon repairs (FTRs), and to identify factors correlating with opioid use over the 90-day postoperative period.

Methods: Using the 2010 to 2020 M165Ortho PearlDiver Mariner Patient Claims Database, patients undergoing primary zone II FTRs were identified. Exclusion criteria were patients with prior opioid use or concurrent injuries. Demographic, clinical, and opioid prescription data were analyzed using multivariate linear analysis to assess trends in opioid use and factors correlating with prescribing patterns over the 90-day postoperative period.

Results: Of 19,574 patients, opioids were prescribed for 72.1% (14,117). Among those prescribed opioids, the mean±standard deviation number of prescriptions was 2.0±1.1 and mean morphine milligram equivalents (MME) prescribed was 239.5±305.2.Over the years of the study, the precent receiving opioids remained similar, but of those receiving opioids, the number of prescriptions declined (2.3 to 1.6, $p < 0.001$) and MMEs declined (from 350 to 200, $p < 0.001$). Factors associated MMEs prescribed included older age, male sex, higher comorbidity (ECI), and geographic region.

Conclusion: Despite a decline in opioid quantity per patient, most patients still receive opioids after zone II FTR. Demographic factors associated with MMEs prescribed may suggest different needs for different cohorts, but regional factors suggest room for more consistent pain management strategies.

MISSED OPPORTUNITIES FOR MULTIDISCIPLINARY EVALUATION IN SEVERE PRIMARY MITRAL REGURGITATION

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Introduction: Multidisciplinary evaluation is known to improve outcomes in various cardiovascular diseases, including severe primary MR. The aim of this study was to compare characteristics and outcomes of patients with new severe primary MR, contrasting those who did and did not undergo multidisciplinary evaluation.

Methods: We conducted a retrospective cohort study of patients with new diagnoses of severe primary MR in a large healthcare network between 2016-2020. Characteristics and outcomes of patients who did and did not undergo multidisciplinary evaluation were compared. Mode of death was classified as cardiac, neurologic, infectious, malignancy, or other/unknown, based on medical record and death certificate reviews. Two-year survival was estimated using Kaplan-Meier analysis.

Results: There were 391 unique patients with severe primary MR. Unevaluated patients were older (median age of 85 years [IQR 75, 90] vs. 74 [IQR 63,81], p<0.001) and more predominantly female (N=78/119, 66% vs. N=102/272, 38%, p<0.001). Unevaluated patients had higher STS PROM for MV repair than evaluated patients (3.8% [IQR 1.3, 7.4) vs. 1.2% [IQR 0.5%, 3.4%], p<0.001), reflected by more prevalent comorbidities: rheumatic disease (2.6% vs 13%, p <0.001), previous MI (12% vs 5.5%, p=0.03), dementia (5.9% vs 1.1%, p= 0.011), and liver disease (3.4% vs 0.4%, p= 0.032). Evaluated patients had lower all-cause mortality than unevaluated patients at 90-days and 2-years (N=19/272, 7% vs. N=32/119, 27%, p <0.001; N=41/272, 15% vs. N=55/119, 46%, p <0.001 respectively). Unevaluated patients were less likely to die due to a cardiac cause and heart failure than evaluated patients (N=20/55, 36% vs N=27/41, 66%, p <0.001; N= 19/55, 35% vs N = 23/41, 56% p= 0.035 respectively). Unevaluated patients had a high proportion of non-cardiac causes of death (64%), which included infectious (N=15/55, 27%), neurologic (N=7/55,13%), and cancer (N=8/55, 15%) etiologies. Among unevaluated patients, 14% (N= 17/119) had an STS PROM < 1% while 33% (N=39/119) had an STS PROM < 2%, representing the low surgical risk patient group.

Conclusion: Patients with severe primary MR who underwent multidisciplinary evaluation had lower mortality rates, with cardiovascular death being the leading cause. A higher proportion of non-cardiac causes of death among unevaluated patients suggests that there is a functional upstream triaging prior to referral for multidisciplinary evaluation based on perceived risk of competing mortality factors. Concurrently, there were low-risk patients with severe primary MR that were not evaluated, highlighting the need for a more systematic approach.

EPIGENETIC THERAPY SENSITIZES ANTI–PD-1 REFRACTORY HEAD AND NECK CANCERS TO IMMUNOTHERAPY RECHALLENGE

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Introduction: Immune checkpoint blockade (ICB) is an effective treatment in a subset of patients diagnosed with head and neck squamous cell carcinoma (HNSCC); however, the majority of patients are refractory. Increasing evidence highlights the tumor's overall poor antigenicity and innate and adaptive immune suppressive mechanisms as key contributors to these refractory responses. In this clinical study, we hypothesized that epigenetic reprogramming through the administration of a low-dose DNA methyltransferase inhibitor, 5-azacytidine (5-aza), can improve tumor antigenicity through epigenetic modulation of immune suppressive cells and the reexpression of epigeneti-cally silenced HLA class I APM components and/or immuno-genic tumor antigens (TAs) to improve clinical outcomes upon rechallenge with immune checkpoint blockade (ICB)

Methods: In a nonrandomized, open-label Phase 1b clinical trial, participants with recurrent and/or metastatic (R/M) HNSCC were treated with low-dose 5-azacytidine (5-aza) daily for either 5 or 10 days in combination with durvalumab and tremelimumab after progression on ICB. The primary objective was to assess the biologically effective dose of 5-aza as determined by molecular changes in paired baseline and on-treatment tumor biopsies; the secondary objective was safety.

Results: Thirty-eight percent (3 of 8) of participants with evaluable paired tissue samples had a greater-than 2-fold increase from baseline in IFN-γ _signature and CD274 (programmed cell death protein 1 ligand, PD-L1) expression within the tumor microenvironment (TME), which was associated with increased CD8+ T cell infiltration and decreased infiltration of CD4+ T regulatory cells. The mean neutrophil-to-lymphocyte ratio (NLR) decreased by greater than 50%, from 14.2 (SD 22.6) to 6.9 (SD 5.2). Median overall survival (OS) was 16.3 months (95% CI 1.9, NA), 2-year OS rate was 24.7% (95% CI: 4.5%, 53.2%), and 58% (7 of 12) of treated participants demonstrated prolonged OS of greater than 12 months.

Conclusion: Our findings suggest that low-dose 5-aza can reprogram systemic host immune responses and the local TME to increase IFN-γ _and PD-L1 expression. The increased expression of these established biomarkers correlated with prolonged OS upon ICB rechallenge.

UNDERSTANDING THE IMPACT OF SOMATIC MUTATIONS ON TREATMENT OUTCOMES AND OVERALL SURVIVAL IN ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

Parisa Abedi, Andrew George, Ben Schiff, Soraya Fereydooni, Andres Aguirre, Benjamin Judson, Saral Mehra, Curtis Pickering

Introduction: The genomic alterations in head and neck squamous cell carcinoma (HNSCC) have been characterized by The Cancer Genome Atlas (TCGA) and other sequencing projects. However, no genomic alterations are used for patient treatment selection in this disease, even though many have been shown to be associated with patient outcomes and response to therapy. For example, two different TP53 mutation scoring systems have been associated with outcomes following cisplatin-containing therapy

Methods: This study analyzed the Flatiron Health Clinico-Genomic Database (CGDB) for HNSCC. The aim was to conduct a comprehensive analysis of genetic alterations in HNSCC and their correlations with treatment and overall survival. Analyses focused on mutations in frequently mutated genes such as TP53, NOTCH1, PIK3CA, and others. Associations with demographic variables and disease characteristics like HPV status were also performed. Since the sequences samples were often collected from metastatic lesions instead of primary tumors, confounding variables, such as selection bias were considered.

Results: This CGDB cohort is biased toward patients with recurrent or metastatic HNSCC, therefore the demographics and genomic alterations are different than those of primary tumors. Mutations in specific genes were found to be associated with overall survival alone or in patients treated with specific adjuvant therapies.

Conclusion: The integration of clinical and genomic data offers valuable insights into the factors affecting survival rates among patients with HNSCC. Identifying specific genomic alterations that impact response to therapy can guide personalized treatment strategies and improve patient management.

THE FIVE-ITEM MODIFIED FRAILTY INDEX (MFI-5) PREDICTS ADVERSE SHORT-TERM OUTCOMES IN PATIENTS UNDERGOING MASTECTOMY: A PROPENSITY SCORE-MATCHED ANALYSIS OF 252,054 CASES

Klimitz, F.J., Diatta, F., Freeman, J., Schaschinger, T., Brown, S., Knoedler, S., Hundeshagen, G., Kauke-Navarro, M., Panayi, A.C., Pomahac, B.

Introduction: Frailty has emerged as a crucial predictor of postoperative outcomes, particularly in surgical patients. However, its role in mastectomy patients remains underexplored. The 5-item Modified Frailty Index (mFI-5) has been increasingly used to assess frailty in surgical populations. This study evaluates whether the mFI-5 predicts 30-day postoperative complications in mastectomy patients, aiming to enhance preoperative risk stratification and inform clinical decision-making.

Methods: A retrospective cohort study was conducted using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) between 2008 and 2022. Female patients undergoing mastectomy were categorized into high-risk (mFI-5 ≥2) and low-risk (mFI-5 <2) groups. Propensity score matching (PSM) was applied to create comparable cohorts. Multivariate logistic regression was used to evaluate associations between frailty and postoperative outcomes, including overall complications, surgical site infections, unplanned readmissions, and reoperations.

Results: Among 252,054 mastectomy patients, 1.2% were classified as high-risk frail. These patients were older (70±9.9 vs. 60±14 years, $p<0.001$) and had a higher BMI (35±9.1 vs. 29±7.1 kg/m², $p<0.001$). After PSM, high-risk frail patients demonstrated significantly increased odds of: Any complication (OR: 2.05, 95% CI: 1.70–2.47, $p<0.001$), Surgical complications (OR: 1.70, 95% CI: 1.38–2.10, $p<0.001$), and Medical complications (OR: 3.81, 95% CI: 2.64–5.50, $p<0.001$). Key complications included wound infections, bleeding requiring transfusion, and sepsis. Additionally, high-risk patients had significantly higher odds of unplanned readmissions (OR: 3.29, $p<0.001$) and reoperations (OR: 1.59, $p=0.006$).

Conclusion: The mFI-5 is a robust predictor of postoperative complications in mastectomy patients, reinforcing its role in preoperative risk stratification. Integrating frailty assessment into routine clinical practice can guide surgical decision-making, optimize resource allocation, and improve patient outcomes. Future studies should explore long-term complications and interventions to mitigate frailty-associated risks.

CANCER-RELATED LYMPHEDEMA AND ALZHEIMER'S DEVELOPMENT AFTER ALND: IS THERE A LINK?

Brown S, Klimitz F, Kauke-Navarro M, Noel O, Wo L, Haykal S, Pomahac B

Introduction: Emerging evidence suggests that glymphatic system dysfunction contributes to amyloid-beta deposition and the progression of Alzheimer's Disease (AD). In animal models, impaired meningeal lymphatic drainage has been linked to cognitive decline, while restoring lymphatic function has improved cognitive outcomes. Axillary lymph node dissection (ALND) is a major risk factor for cancer-related lymphedema, yet its potential link to AD remains unexplored. This study investigates the association between lymphedema and AD development following ALND.

Methods: We conducted a longitudinal analysis of 15,666 patients who underwent ALND at a tertiary cancer center from 2013 to 2024. Demographic and clinical data, including lymphedema diagnosis and AD onset, were collected. A multivariate regression model was used to assess risk factors for AD after ALND and evaluate the relationship between lymphedema and AD development.

Results: Of the 15,666 patients, 2,345 (14.9%) developed lymphedema, with a mean onset of 20.5 months post-ALND. Among the 8,095 patients aged 60 or older at the time of ALND, 243 (3%) developed AD. Significant predictors of AD included older age at ALND (OR=1.1, 95% CI 1.089–1.129, p<0.0001), cerebrovascular disease (OR=6.1, 95% CI 1.203–2.222, p=0.0016), preexisting depression (OR=3.6, 95% CI 2.704–4.789, p<0.0001), African American race (OR=1.817, 95% CI 1.162–2.752, p=0.0065), and Hispanic/Latino ethnicity (OR=2.116, 95% CI 1.270–3.378, p=0.0026). Lymphedema diagnosis was associated with a lower risk of AD (OR=0.3, 95% CI 0.1679–0.6240, p=0.0013).

Conclusion: This is the first and largest study to investigate the relationship between cancer-related lymphedema and AD following ALND. While known risk factors for AD were confirmed, the unexpected inverse association between lymphedema and AD warrants further research. Future studies should explore the potential influence of lymphatic dysfunction and extremity lymphedema treatment on neurodegenerative pathways and cognitive outcomes.

A COMPARATIVE ANALYSIS OF LESIONAL SKIN, SENTINEL FLAP, AND MUCOSAL BIOPSIES IN ASSESSING ACUTE FACE TRANSPLANT REJECTION

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Introduction: Face transplant rejection is primarily monitored through skin biopsies, but mucosal biopsies may detect immune rejection events missed by skin samples, raising concerns about relying solely on cutaneous assessments. This study evaluates the correlation between rejection grades in mucosal, facial skin, and sentinel flap biopsies, aiming to improve rejection monitoring protocols in facial vascularized composite allotransplantation (fVCA).

Methods: A retrospective review of 47 paired mucosal and facial skin biopsies and 37 paired facial skin and sentinel flap biopsies was conducted from nine face transplant recipients. Rejection was graded using the 2007 Banff classification for skin and an adapted grading system for mucosa. Statistical analysis included correlation assessments, sensitivity and specificity metrics, and predictive value calculations.

Results: Mucosal and facial skin rejection grades correlated strongly ($r = 0.72$, $p < 0.0001$), with mucosal biopsies demonstrating a negative predictive value (NPV) of 0.85 for skin rejection. Mucosal biopsies identified rejection in 10 cases missed by facial skin biopsies, while isolated skin rejection was rare and clinically insignificant. Sentinel skin biopsies correlated well with facial skin biopsies but had an NPV of 0.76, missing 25% of rejection cases.

Conclusion: Including mucosal biopsies provides a more sensitive and reliable method for detecting rejection in face transplants compared to skin biopsies alone. The findings support incorporating mucosal biopsies into routine rejection monitoring, as they offer a broader assessment of immune activity. Sentinel skin biopsies showed limited reliability in predicting facial skin rejection and may not serve as a substitute for direct tissue sampling.

FACIAL SUBUNIT TRANSPLANTATION: CURRENT CONCEPTS AND FUTURE DIRECTIONS

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Introduction: Complex facial defects resulting from trauma, cancer, or congenital genital disorders present significant challenges for reconstructive surgery. Traditional methods, such as local flaps and grafts, often yield suboptimal aesthetic and functional outcomes. Facial vascularized composite allotransplantation (fVCA) has become a valid option for extensive facial defects. The isolated transplantation of facial subunits potentially allows for a targeted restoration of smaller defects of individual subunits, which is currently not implemented in clinical practice. Moreover, this approach focuses only on the damaged subunit, reducing invasiveness and minimizing further tissue loss in case of graft failure.

Methods: A literature review was conducted using three electronic databases (PubMed, Embase, and Google Scholar) with no restrictions to identify relevant literature on facial subunit transplantation. Keywords included “facial subunit transplantation,” “vascularized composite allotransplantation,” “immunosuppression,” “animal models,” and “cadaver studies.” Inclusion criteria included animal model studies, cadaver studies, clinical experiences, and studies that described at least one of the following: surgical technique, vascular anatomy, rejection dynamics, and translational applications. Studies without detailed methodology or insufficient focus on facial subunits were excluded.

Results: Subunit transplantation appears to be anatomically feasible with established pedicle options for specific regions. Preclinical studies detailed vascular supply dynamics and rejection in transplanted tissues, particularly among primate and rat models. The studies emphasized a need for optimized immunosuppressive management to prolong graft survival, demonstrating the requirement for immunosuppression protocols similar to full-face transplantation. Cadaveric studies focused on vascularization strategies for facial subunits, revealing adequate vascularization may be achieved in subunits with the facial artery as the main pedicle.

Conclusion: The findings of this literature review indicate the potential for facial subunit transplantation to offer improved outcomes in select cases of facial reconstruction, particularly in functional and aesthetic-critical subunits. Addressing challenges in immunosuppression and vascular planning may position subunit transplantation as a less invasive alternative for specific patient populations with tailored benefits regarding localized facial defects.

FINANCIAL OUTLOOK THROUGH CANCER STORYTELLING (FORECAST): PATIENT- STORYTELLING INTERVENTION TO MITIGATE FINANCIAL HARDSHIP IN BREAST CANCER CARE

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Introduction: Treatment-related financial hardship impacts 35% of individuals with cancer. Despite available financial resources, stigma around the unaffordability of cancer care, the distress of a life-threatening diagnosis, and the unexpectedness of cancer treatment costs remain barriers to support. Narrative storytelling promotes positive health behaviors and connects women to resources. The FOReCAST study aims to test patient-to-patient testimonials as a novel intervention to protect young women against breast cancer related financial hardship.

Methods: We developed a novel video-based intervention through recruitment of women 45 years within 5 years from a diagnosis of stage 0-IV breast cancer who self-reported breast cancer related financial hardship. Participants were recruited from the Yale Smilow Cancer Center and local breast cancer support groups. Women participated in two three-hour storytelling workshops led by SpeakUp Storytelling and a therapist and were compensated for their time. Pre-workshop, participants completed a 34-item survey adapted from validated survey tools (COST-FACIT; FACT-B). Survey data were analyzed using descriptive methods.

Results: Overall, N=8 women participated; ages ranged from 29 to 45. Three women self-identified as White, three as Black, one as Hispanic White, and one as Puerto Rican. At diagnosis, 75% of women reported experiencing cancer-related financial hardship; 62.5% reported feeling “very much” financially stressed during treatment and 62.5% were unable to meet monthly expenses. At diagnosis, 86% of participants were insured (57% employer-based, 14% Medicaid, 14% Medicare) and 14% uninsured. This changed during cancer treatment with 100% of patients reporting insurance (29% employer-based, 29% Medicaid, 43% Medicare). Notably 50% of participants reported that costs of care did not impact their cancer treatment decisions, while 39% reported it impacted their choices significantly. Cost coping strategies were identified and shared during the workshop and included: negotiating housing prices, use of government financial assistance programs, navigating employment, and child-care during treatment. Participants reported satisfaction with their experiences in the storytelling workshops, specifically noting that sharing helped them feel less alone, the benefit of hearing coping strategies from peers, their excitement to help others, and the cathartic experience of processing and writing their own stories.

Conclusion: Narrative storytelling is a novel, patient-centered approach to destigmatize cancer-related financial hardship, empower patients in their care, and communicate cost-coping strategies that hold promise to mitigate financial hardship for women with breast cancer. The FOReCAST tool will be tested for feasibility, acceptability, and preliminary efficacy as part of the Smilow Cancer Hospital Early Onset Breast Cancer Pathway among early onset breast cancer patients.

THE HAZARDS OF A DRINK IN HAND: A CRITICAL ASSESSMENT OF THE EPIDEMIOLOGY OF HAND INJURIES INVOLVING DRUGS AND ALCOHOL

Aliyar Zahedi Vafa,Sam Boroumand, Ismail Ajjawi, Felix J. Klimitz, Beatrice Katsnelson, Nancy Park, Gabriel Carrillo, Adnan Prsic

Introduction: Alcohol and drug use contribute significantly to the morbidity and mortality of traumatic injuries. The purpose of this study is to explore the impacts on drugs/alcohol on the epidemiology of traumatic hand injuries in the U.S.

Methods: The National Electronic Injury and Surveillance System (NEISS) database was queried from 2019-2022 to identify patients admitted to the emergency department (ED) with reported hand injuries. Patients with alcohol/drug involvement at the time of their injury were isolated as a separate comparison group. Variables including sex, race, products involved in injury, and ED disposition were assessed between the two patient cohorts utilizing two-proportion z-tests.

Results: In total 202,979 patients with traumatic hand injuries were identified with 3,013 cases involving drugs and/or alcohol. Laceration injuries occurred at a significantly higher frequency in cases involving drugs/alcohol than those that did not (43.4% vs. 35.2%, $p< 0.001$) followed by contusions (10.4% vs. 8.7%, $p= 0.001$) and avulsions (3.4% vs. 2.2%, $p< 0.001$). The most common cause of hand injury in both populations was knives, with cases involving drug/alcohol injuries incurring at a higher frequency than injuries with no drug/alcohol involvement (11.7 % vs. 10.1%, $p=0.007$). The overall odds ratio of hospital admission following hand injury for cases that involved alcohol/drugs (relative to those that did not) was 5.2 (95% CI: 4.6-5.9, $p<0.001$)

Conclusion: The likelihood of hospitalization following hand injury is over five-fold greater under the influence of drugs/alcohol, with a significantly greater frequency of specific injury types/etiologies. Ultimately, these epidemiological findings can be leveraged to provide hand surgeons invaluable qualitative context for the most frequent presentations of hand injuries they can anticipate to treat among intoxicated patients.

STRUCTURES INVOLVED IN ENDOSCOPIC CARPAL TUNNEL SYNDROME RELEASE: AN ANATOMICAL STUDY OF THE WRIST

Aliyar Zahedi Vafa, Ismail Ajjawi, Omar Allam, Adnan Prsic

Introduction: Endoscopic Carpal Tunnel Syndrome Release (CTSR) is a recurrent operation, accounting for over one-fourth of Carpal Tunnel Syndrome Release procedures1. Nonetheless, wrist anatomy presents knowledge gaps that could improve the precision and safety of the procedure.
This study investigates the anatomy of the wrist, specifically exploring ratios and relationships of key anatomical landmarks used in CTSR. We aim to develop a tool that provides surgeons with accurate and reliable anatomical references, therefore improving outcomes for this commonly performed procedure.

Methods: Post-mortem cadaveric dissections were performed on bilateral wrists and hands in 5 human cadavers in the anatomy laboratory of Yale School of Medicine. The cadaveric subjects were examined to measure the distances between landmarks and characterize their ratios. Three independent authors (A.Z.V., O.A., and A.P.) took and assessed the measurements.

Landmarks:

- Pisiform
- Flexor carpi radialis muscle tendon intersection with the wrist crest
- Hook of the hamate
- Perpendicular intersection of the hook of the hamate with the wrist crest
- Median nerve

Ratios:

- Distance between 1 and 4 divided by the distance between 1 and 2
- Distance between 1 and 5 divided by the distance between 1 and 2
- Distance between 3 and 4 divided by the distance between 1 and 4

For each ratio, the mean and 95% confidence interval (CI) were calculated for the left and right hands, and a Mann-Whitney U test was performed to evaluate eventual differences between sides.

Results: For the first ratio, no significant difference was observed between the mean ratio of the left and right sides (0.464 [95% CI = 0.223, 0.705] vs 0.389 [95% CI = 0.244, 0.534], p = 0.753).

For the second ratio, no significant difference was observed between the mean ratio of the left and right sides (0.681 [95% CI = 0.568, 0.794] vs 0.652 [95% CI = 0.550, 0.754], p = 0.675).

For the third ratio, no significant difference was observed between the mean ratio of the left and right sides (1.7856 [95% CI = 0.3346, 3.2366] vs 1.8748 [95% CI = 0.8718, 2.8778], p = 0.69).

Conclusion: This study demonstrates no significant difference between the left and right hand ratios, suggesting consistency on both sides and establishing predictable anatomical ratios. This can provide surgeons with a useful tool for preoperative planning. By confidently mapping anatomical landmarks, surgeons can operate more safely and effectively, reducing the risk of injuring critical structures.

HIGH RATES OF SYNCHRONOUS ONCOCYTIC NEOPLASMS AND PAPILLARY THYROID CARCINOMAS: ARE WE MISSING SOMETHING?

Haynes CV., Mahoney FS., Rome C., Ladenheim A., Ramirez AG.

Introduction: Oncocytic carcinoma (OC) is rare, comprising 2-4% of thyroid carcinomas. Due to its low prevalence and limited research, the drivers of OC are unknown. Papillary thyroid carcinoma (PTC) incidence in cadaveric studies is 11-13%, but the coexistence of PTC and OC has not been described. We observed a higher incidence of concurrent PTC with oncocytic neoplasms (ON) and hypothesized that this relationship represents a causal effect.

Methods: A single-institutional pathology database was queried for all patients diagnosed with OC and oncocytic adenomas (OA) between 2012-2022. Analysis was performed on 120 patients. Patients were categorized according to pathology concurrence and according to concurrence sharing an anatomic locus (homotopy) or concurrence not sharing an anatomic locus (heterotopy). Univariate and descriptive statistics were performed assessing differences in patient clinical presentation and molecular profiles.

Results: Of the 42 patients with OC, 14 had concurrent PTC (33.3%). Of the 79 patients with OA, 21 had concurrent PTC (29.1%). There was no difference in the incidence of concurrent PTC between patients with OA and OC ($p=0.68$). 50.0% of male patients had OC while 29.5% of female patients had OC ($p=0.05$). Patients with OC also had a larger tumor size than patients with OA (3.9cm vs 2.3cm, $p<0.001$), though patients with concurrent PTC did not have a larger tumor size (2.9cm~2.8cm, $p=0.93$). Among those with concurrent PTC, the size of PTC did not differ between those with OC or OA (0.9cm~0.6cm, $p=0.47$). Among patients with all thyroid tissue available for analysis, the prevalence of homotopic PTC compared to heterotopic was not significant (19/61>16/61, $p=0.69$). Among 51patients with molecular testing corresponding to an ON, the most identified genetic variations were NRAS (7/51), copy number variations (7/51), and EIF1AX (4/51). The distribution of molecular and genetic variations identified by preoperative molecular testing did not differ between +/- concurrent PTC, +/-homotopic PTC, patients with OA, and those with OC. The risk of malignancy as determined by molecular testing did correlate with the prevalence of oncocytic malignancy, though the correlation was not statistically significant ($p=0.09$).

Conclusion: PTC concurrence among patients with ON, managed operatively, is significantly higher than the prevalence reported among the those managed for different pathology. Current genetic tests are poor predictors of malignancy risk for oncocytic tumors and molecular testing results were not predictive of risk of PTC concurrence. Further research into this synchronous relationship and molecular and potential environmental drivers is warranted.

EX-VIVO PARATHYROID ASPIRATION IN PARATHYROIDECTOMY: CORRELATION WITH HISTOPATHOLOGY AND BIOCHEMICAL OUTCOMES IN SINGLE- AND MULTI-GLANDULAR HYPERPARATHYROIDISM

Merchant, N., Kodger, J., Ogilvie J., Gibson C., Durant T., Ramirez A.

Introduction: Surgical treatment of hyperparathyroidism is often supported by intraoperative adjuncts for parathyroid tissue confirmation. Ex vivo aspiration of excised parathyroid tissue followed by intraoperative parathyroid hormone testing (aIOPTH) is a rapid and sensitive technique that can discriminate between parathyroid and surrounding tissues. There is limited literature regarding specific aIOPTH protocols, correlation with final histopathology, and the impact of its use on patient outcomes. This study aims to describe the implementation and effectiveness of an aIOPTH protocol.

Methods: This observational, retrospective study was conducted at a tertiary care academic hospital. It included patients who underwent parathyroidectomy with aIOPTH testing between June 2023 and August 2024. Quantitative aIOPTH values were converted to qualitative results (‘positive’ or ‘negative’) based on absolute cutoffs of 500 and 5,000 pg/mL. These qualitative results were then compared to final histopathology findings from the excised tissue. Performance metrics were calculated from this comparison. Additionally, subgroups of patients with adenomatous versus multiglandular disease were similarly analyzed. Six-month postoperative cure rates were assessed using total calcium levels.

Results: This study included 55 patients undergoing parathyroidectomy, during which 123 unique aIOPTH specimens were analyzed. Using the 500-cutoff, sensitivity was 98% and positive predictive value (PPV) was 96%. With the 5,000-cutoff, sensitivity decreased to 88%, while PPV increased to 99%. Of the 22 patients with multiglandular disease (n=22), 70 unique aIOPTH specimens were analyzed. In this subgroup, sensitivity and PPV were 97% and 95% for the 500-cutoff, and 88% and 100% for the 5,000-cutoff, respectively. At the time of this analysis, 96.6% of patients with who had six-month postoperative calcium testing (n=29) demonstrated durable biochemical cure.

Conclusion: The use of an absolute cutoff in aIOPTH testing protocols shows clinical performance comparable to that reported in current literature. Lower absolute PTH cutoffs enhance sensitivity without a significant decline in PPV. Additionally, aIOPTH performs similarly in patients with intraoperatively identified multiglandular disease. Moreover, aIOPTH was associated with a high rate of biochemical cure. These findings support the use of ex vivo aspiration for intraoperative parathyroid testing as an effective aid for intraoperative decision-making.

LOCAL INFRASTRUCTURE AND ECONOMY PREDICTS TRAFFIC RELATED FATALITIES IN CHILDREN

Hellmann ZJ, Graetz E, Rehman S, Moore M, Schneider EB, Christison-Lagay ER, Solomon DG

Introduction: Previous research on pediatric motor vehicle collisions (MVC) and fatalities has primarily focused on patient demographics and crash specific information. This study evaluates whether various measures of local infrastructure, including the National Walk Index (NWI), population density, and public school density, or macroeconomic forces, encapsulated in Social Vulnerability Index (SVI) and food area deprivation (PFA) can predict which counties are most at risk for pediatric traffic fatalities.

Methods: Counties with more than 100,000 children in the most recent US census and ≥1 pediatric traffic fatality as identified in the Fatality Analysis Reporting System (FARS) between 2017-2021 were included in the study. Poisson regression modeling was used to identify county level infrastructure and macroeconomic forces that predicted increasing MVC related average annual mortality rate per 100,000 children.

Results: There were 158 counties that met inclusion criteria. Univariate Poisson regression demonstrated that NWI, SVI, PFA, population density, and school density each individually correlated with MVC related mortality rate ($p < 0.001$ for all predictors). When controlling for SVI and population density, multivariable Poisson regression demonstrated that each decile increase in walkability was associated with a 7% decrease in MVC related mortality rate (IRR 0.93, 95% CI 0.91-0.96).

Conclusion: Areas with poor walkability predict the likelihood of pediatric traffic fatality. These findings highlight tangible local and state policy changes that could be implemented to decrease the likelihood of traffic-related child fatality rates in specific counties.

ARNOLD SCHWARZENEGGER OR DANNY DEVITO? THE FATE OF TWINS WITH NECROTIZING ENTEROCOLITIS IN THE NICU

Sapir NG., Hellmann ZJ., Rehman S., Cowles RA., Christison-Lagay ER, Solomon D.

Introduction: Previous literature suggests infants of multiple gestation pregnancies have a higher incidence of necrotizing enterocolitis (NEC) than singleton gestations. However, no study has examined the likelihood of co-incident NEC among multiples. We hypothesize there would be an increased incidence of NEC among multiples whose siblings had been diagnosed with NEC.

Methods: The Pediatric Health Information System was queried for all neonatal intensive care unit (NICU) admissions between 2017-2023. Patients with incomplete gestational age or birth weight information were excluded, and internal validation of data was performed. Multiple gestational sets were identified by diagnostic code indicating multiple gestation, and matched hospital center, birthdate, race/ethnicity, and deidentified zip code. Univariate and multivariate logistical regression was performed to assess the likelihood of developing NEC if one sibling in a multiple set was diagnosed with NEC.

Results: There were 253,577 NICU infants included, and 11,396 individuals (4.49%, 4,011 groupings) with a diagnostic code indicating a multiple gestation pregnancy. Multiples had shorter gestations (32.3 vs 35.8 weeks, $p<0.01$), lower birthweights (1811.6 vs 2711.4 grams, $p<0.01$), and developed NEC more frequently (3.9% vs 2.6%, $p<0.01$) than an uncontrolled cohort of NICU singleton births. However, when controlling for gestational age, birth weight, gender, and congenital heart defect, multiples were less likely than singleton births to develop NEC (OR 0.77, 95%CI 0.70-0.85). Nevertheless, if one infant in a set of multiples developed NEC, a second sibling was more likely to develop NEC compared to the general NICU population (16.4% vs 2.6%, $p<0.01$). This correlation remained significant when controlling for gestational age and average birthweight of the multiple set (OR 1.70, 95%CI 1.22-2.38).

Conclusion: We conclude that infants born of multiple gestational pregnancies are less likely to develop necrotizing enterocolitis as compared to a cohort of singleton infants admitted to the NICU. However, if one infant in a set of multiples develops necrotizing enterocolitis, there is a significant increase in likelihood that another sibling will develop necrotizing enterocolitis. It is unclear from present data whether this is related to genetic/microbiomic predisposition or hospital infrastructure that groups multiples in proximal rooms/beds subjecting them to similar infectious risks.

GEOGRAPHIC DISTRIBUTION OF PREAS IN CONNECTICUT AND CORRELATION WITH INCOME AND POPULATION

Alexander R Neifert, David G. Su, Bauer E. Sumpio

Introduction: Traditional atherosclerosis (TradAS) has historically been defined as a disease that impacts patients over the age of 50. We sought to better understand what individuals are at the highest risk for premature atherosclerosis (PreAS) within Connecticut. In particular, we examined variations by zip code in household income and population to better understand the potential relationship with premature disease.

Methods: Data from a large regional health system was evaluated under IRB approval. A retrospective chart review was performed on records for all patients from 2012-2023 with ICD 10 diagnosis of cerebrovascular disease (CeVD), coronary artery disease (CAD) or peripheral arterial disease (PAD) including their relevant subcategory codes. We then paired this data with 2020 US Census Data including population and median household income data. Zips with fewer than 50 patients, and non-reporting zip codes for Census data were excluded from analysis. Threshold for maximum recorded household income for Census data was $250,000.

Results: For our data, the mean ratio of PreAS to TradAS was 0.13 with a range from 0.02 to 0.4. The median household income for all included zip codes was $104,443 with a range from $16,000 to $250,000+ . Four zip codes reported a median household income above $250,000. The median population by zip code was 8,268 with 30 zip codes reporting a population less than 1,000 and the highest population reported at 67,879. There was a positive Pearson correlation coefficient of 0.35 between the population in a zip code and the ratio of PreAs to TradAS. There was a negative Pearson correlation coefficient between median household income and the ratio of PreAs to TradAS.

Conclusion: Our study shows a positive correlation between increased population and an increase in the ratio of patients diagnosed with PreAS and a negative correlation between household income and PreAS. These are moderate correlations and further studies are needed to better understand the distinct subpopulations and potential environmental characteristics leading to these findings.

OUTCOMES OF MECHANICAL THROMBECTOMY FOR ACUTE LIMB ISCHEMIA AT A TERTIARY REFERRAL CENTER

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Introduction: Acute limb ischemia (ALI) historically harbors high risk of limb loss and mortality. Modern algorithms for ALI have incorporated mechanical thrombectomy devices. A recently published prospective, multi-institutional, industry-sponsored study demonstrated high rate of limb salvage and low complication rates at 30 days with the IndigoTM Aspiration System. The aim of the current study was to examine patient outcomes in a “real-world” experience with mechanical thrombectomy (MT) for ALI.

Methods: ALI cases with duration of symptoms <2 weeks and treated with mechanical thrombectomy at a tertiary referral center between 2016-2024 were reviewed. Primary outcomes were 30-day and 1-year freedom from major amputation. Secondary outcomes were mortality and major adverse cardiovascular event (MACE) at 30 days, need for adjuvant thrombolysis, conversion to open surgery, and major bleeding events.

Results: 70 patients (73 limbs) with mean age 67 years (range 32-105 years) had a median follow-up of 297 days [0-2554]. Rutherford Class was I 46.6%, IIa 30.1%, IIb 20.6%, III 0%, and unknown 2.7%. Etiology was thrombosis or embolism of native artery in 46 limbs, thrombosed bypass in 14 limbs, and thrombosed stents in 13 limbs. 42.5% had adjuvant overnight catheter-directed thrombolysis and 15.1% were converted to open surgery. 91.8% of limbs required adjuvant procedures (61 angioplasty, 33 stenting, 11 prophylactic and 4 delayed fasciotomies) during or after the index procedure. Device used was Penumbra Indigo® 61.6% (45/73 limbs), AngioJetTM 32.9% (24/73), and both 5.5% (4/73). 30-day and 1-year freedom from major amputation was 90.9% and 71.7%, respectively. 30-day complications were 8.2% mortality, 9.6% MACE, and 6.8% major bleeding events.

Conclusion: Overall freedom from amputation after mechanical thrombectomy was 90.9% at 30 days which is comparable with a recent multicenter trial, although with a higher rate of adjuvant thrombolysis and conversion to open thrombectomy in the current study. Mechanical thrombectomy is an effective treatment for ALI in “real world” practice.

PIK3CA MUTATIONS ARE MORE FREQUENT IN EARLY-ONSET APPENDICEAL CANCER AND ASSOCIATED WITH WORSE SURVIVAL

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Introduction: The incidence of appendiceal cancer (AC) is rising in the US, with a steep rise of 251.89% in early-onset AC (age <50 years) between 2010-2019. Certain mutations like PIK3CA have been reported at a higher frequency in early-onset AC, but data regarding their implications on survival is lacking. This study aims to compare the mutational profiles of early-onset and late-onset AC and assess their impact on survival outcomes.

Methods: A retrospective analysis of AC patients from the Memorial Sloan Kettering – Metastatic Events and Tropisms (MSK-MET) database was conducted. Patients were stratified into two groups: early-onset (<50 years) and late-onset (≥50 years) AC based on age at surgery. Pearson's Chi-squared test was used to compare categorial variables, while logistic regression was used to evaluate the mutational profile differences. Kaplan-Meier survival analysis and Cox proportional hazards regression were performed for survival associations.

Results: Of 200 patients analyzed (median age: 55.4 years, IQR: 47.22-67.75), 35% (70) were early-onset AC. No significant differences in sex, race, histological subtypes, or survival (log rank p = 0.86) were found between early-onset and late-onset AC. Early-onset AC patients had significantly higher odds of harboring PIK3CA mutations compared to late-onset AC (17.6% vs 8.1%, odds ratio [OR] 3.99, p = 0.01) after adjusting for sex, histology, race, and sample type. PIK3CA mutations were exclusively seen in patients with metastatic AC (12.36%) and were more common in non-mucinous than mucinous AC (17.7% vs 7.1%, p=0.04). Among metastatic AC patients, those with PIK3CA mutations had worse overall survival (OS) from surgery (3-year survival probability of 41% vs 70%; hazard ratio = 2.65, 95% CI 1.33-5.30, p-value = 0.006).

Conclusion: Early-onset AC patients showed a higher likelihood of having PIK3CA mutations, which negatively impacted survival after surgery. These alterations are targetable, and their prognostic impact should be considered when designing clinical trials involving patients with AC, especially studies focused on early-onset AC.

AORTIC REMODELING WITH ENDOVASCULAR TREATMENT VERSUS MEDICAL THERAPY FOR UNCOMPLICATED ACUTE TYPE B DISSECTION

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Introduction: The most optimal initial management for uncomplicated acute type B aortic dissection (uATBAD) remains unclear. We evaluated one-year aortic remodeling and clinical outcomes of patients undergoing thoracic endovascular aortic repair (TEVAR) versus exclusively optimal medical therapy (OMT) for uATBAD.

Methods: Patients with uATBAD were retrospectively grouped by initial treatment modality with 52 patients treated with TEVAR and 142 with OMT. Patient demographics and outcomes were extracted from patient charts, and aortic remodeling was evaluated using computer tomography angiography scans. Aortic remodeling metrics included change in true lumen diameter (TLD), full lumen diameter (FLD) and true lumen index (TLi), and extent of false lumen thrombosis, and were assessed at 12 thoracoabdominal levels.

Results: The study's average age was 64.6±14.5 years and 38.7% (N=75) were female. TEVAR had lower 30-day/in-hospital mortality than OMT (0% vs 11.3%, $P<0.01$). Reintervention rates did not differ between groups ($P>0.05$). Thirty-one TEVAR and 42 OMT patients were included in remodeling analysis with a median follow-up of 6.9 months (IQR 3.6-10.8). Change in TLD and TLi was greater in TEVAR than OMT from left subclavian artery to the diaphragm ($P<0.001$). Change in FLD showed no difference between groups except at the superior mesenteric artery ($P=0.04$). At the thoracic aortic levels, TEVAR showed significant shift towards full false lumen thrombosis ($P<0.001$).

Conclusion: TEVAR was associated with favorable aortic remodeling as well as short- and mid-term outcomes compared to OMT in patients with uATBAD. The positive remodeling is more pronounced at thoracic aortic levels.

CLINICAL, PHYSIOLOGIC, AND ANATOMIC OUTCOMES OF A NOVEL BIOPROSTHETIC AORTIC VALVED CONDUIT

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Introduction: In 2020 the KONECT aortic valved conduit (AVC) became the first prefabricated bioprosthetic aortic root conduit approved in the U.S. This study assesses its early outcomes in patients undergoing aortic root replacement.

Methods: This single-center retrospective cohort study included patients who underwent an aortic root replacement procedure using the KONECT AVC from November 2020 to December 2023. Of the 140 adult patients identified, 22 were excluded due to emergent procedures, resulting in a final cohort of 118. Clinical data was collected from electronic medical records. Aortic graft dimensions were obtained from initial and latest post-operative computed tomography (CT). Echocardiography functional parameters at preoperative, intraoperative, postoperative and 6-month time interval follow-up was collected. Primary outcomes included operative mortality (within 30 days/in-hospital), late mortality (beyond 30 days), and complications such as stroke, acute kidney injury (AKI), dialysis-requiring renal failure, extracorporeal membrane oxygenation support (ECMO), pacemaker implantation, and aortic reoperation. Secondary outcomes included post-operative valvular function. Anatomic and hemodynamic variables over time were assessed using mixed-effects regression models.

Results: This cohort was predominantly male (108 patients, 91.53%) with a mean age of 63 ±11 years. Surgical indications included root +/-ascending aortic aneurysm (115 patients, 97.46%) and chronic type A dissection (3 patients, 2.54%). Concomitant hemiarch replacement was performed in 109 patients (92.37%), CABG in 23 (19.49%), and mitral valve repair in 6 (5.08%). Median hospital stay was 6.5 days (IQR 5-8), with no operative mortality or stroke. Complications included renal failure requiring temporary dialysis (1, 0.85%), temporary ECMO support (1, 0.85%) and pacemaker implantation (3, 2.54%). Median follow-up was 16.71 months (IQR 11.76-27.60), with 3 late mortalities (2.54%) and 1 aortic reoperation for endocarditis (0.85%). Patients had a post-op transvalvular mean gradient of 7.63 mmHg (SD 3.02) and an ejection fraction of 56.60% (SD 10.20), compared to 8.19 mmHg (SD 2.67) and 61.04% (SD 10.12) at 18 months. Average root diameter of implanted grafts was 37.54 mm (SD 2.38). Post-op CTs showed mean root diameters of 37.63 mm (coronal), 38.80 mm (axial), and 38.56 mm (sagittal). Latest CTs showed stable root dimensions of 37.97 mm, 39.84 mm, and 38.97 mm in these planes.

Conclusion: The KONECT AVC demonstrated excellent short-term clinical, physiologic, and anatomic outcomes. Within the follow-up period the valvular function was satisfactory and anatomic dimensions were stable, though extended follow-up is needed to evaluate the graft's long-term durability.

TUMOR PROFILING AND IMMUNE CELL INFILTRATION OF SEMI-SOLID LUNG NODULES – TRANSLATING PATHOLOGY TO OPTIMIZE SURGICAL DECISION-MAKING

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Introduction: Semi-solid lung nodules(SSN) are common incidental findings on chest CT which pose a clinical dilemma as they often require no treatment but have the potential to become invasive lung adenocarcinoma. Given the limited treatment guidelines, a better understanding of SSN growth patterns and predictors of malignant potential are essential for therapeutic decision-making. This study employs multiplex immunofluorescence(mIF) and spatial transcriptomics using the GeoMx DSP platform to analyze the tumor microenvironment of surgically resected SSNs. These findings are compared to a linked SSN patient database to assess the relationship between radiographic findings, surgical decision-making, pathological features, and patterns of immune cell infiltration.

Methods: H&E section of formalin-fixed paraffin-embedded surgical resections of SSN(n=42) were reviewed by a thoracic pathologist. Specimens underwent mIF with CD8, CD20, and PanCK followed by imaging with Stellaris Confocal Microscope and QuPath cell identification and quantification. DSP evaluated regions of interest for solid, lepidic, and fibrotic areas to investigate RNA and protein expression levels among cell types.To link these findings to surgical decision-making, a large retrospective study was conducted for all patients with SSN identified on radiology reports(n=952) from 2017 at YNHH. Patient demographics, medical history, and radiologic findings were collected. Those with metastatic cancer or suspected infectious, inflammatory, or benign etiology were excluded. The remaining 322 patients underwent multivariate regression analysis.

Results: Among 42 SSNs which underwent mIF and pathology review, most had invasive histology(53%), a lung adenocarcinoma driver mutation(79%), and radiographically demonstrated interval SSN growth(77%) and a solid component(69%). A significant portion had a micropapillary component(22%) and positive lymph nodes(8%). Invasive SSNs exhibited a tumor microenvironment with increased CD8 cells(4.04% vs 2.40%, p=0.11) and CD20 cells(1.26% vs 0.83%, p=0.11). Interestingly, 59% of patients had multiple SSNs on imaging, and their resected SSN had increased CD20 cells(1.24% vs 0.79%, p=0.036) and increased PanCK cells(3.68% vs 2.41%, p=0.11) compared to patients with only a singular SSN on imaging.Multivariate regression of the clinical database revealed SSNs more likely to undergo surgical resection were larger(17.2mm vs 11.6mm, p=0.012) and had developed a new radiographic solid component(78% vs 26%, p<0.001). Factors including SSN growth and presence of multiple SSNs on imaging were not associated with surgery.

Conclusion: This study investigated radiographic changes prior to surgical resection of SSN and explored how these correlated with invasive histology and the tumor microenvironment. Despite size and new solid component being factors in surgical decision-making, these do not necessarily correlate with SSN invasiveness or malignant potential.

DIFFERENCES IN LUNG-RADS SCORING AMONG JUNIOR VS SENIOR RADIOLOGY ATTENDINGS FOR LUNG CANCER SCREENING CT-IMAGING

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Introduction: Variability in radiology attending interpretations of lung cancer screening (LCS) chest CT imaging may arise from differences in experience, subspecialty training, and diagnostic acumen. This study examines differences in Lung-RADS reads for initial LCS CT imaging based on radiology attending demographics and years in practice post-fellowship training.

Methods: A retrospective review of the EMR was performed from a large, tertiary hospital system in the Northeast. All adult patients with a LCS chest CT ordered between Jan 1st, 2022 to December 31st, 2022 were evaluated, as this was the most recent year in the hospital system without attending turnover. Radiologist gender, academic background, and years in practice as an attending (0 to 4 years, 5 to 9 years, >10 years) were collected.

Results: A total of 810 initial LCS CT images were analyzed. Radiology attendings with >10 years of experience were more likely to include other noteworthy findings in their Lung-RADS scoring with a distinguishment of 2S (16.7% for >10 years of experience vs 6.6% for <10 years of experience) or 3S (2.4% for >10 years of experience vs 1.4% for <10 years of experience). Radiologists with 10+ years of practice have a higher tendency to report a completely negative screening exam (Lung-RADS 1) at 27.8% in comparison to radiologists earlier in practice (18.6% for 0 to 4 years post-training, 22.1% for 5 to 9 years post-training).

Conclusion: Differences in radiology attending training background and years in practice may influence Lung-RADS reads for initial CT screening.

SURGERY IS NOT A REQUIREMENT FOR PROLONGED SURVIVAL IN PATIENTS WITH MESOTHELIOMA: A NATIONAL CANCER DATABASE ANALYSIS

Zhan PL., Canavan ME., Bader J., Boffa DJ., Resio B., Woodard GA.

Introduction: Recently, the role of surgery in the treatment of mesothelioma has been called into question. The MARS 2 randomized clinical trial demonstrated no survival benefit from cytoreductive surgery over chemotherapy alone in resectable pleural mesothelioma. We wanted to explore how national practice patterns and outcomes compared to that of the MARS 2 trial. Using the National Cancer Database (NCDB), we investigated the necessity of surgery for long-term mesothelioma survival.

Methods: The NCDB was queried for all adult patients diagnosed with malignant pleural mesothelioma between 2010 and 2018. Kaplan-Meier analysis compared survival across patient cohorts by treatment, including those receiving chemotherapy who declined or forewent a recommended surgery. Survival outcomes were compared to those who underwent chemotherapy and surgery, with and without propensity score matching.

Results: Of 21,768 identified patients with mesothelioma, 9.4% (2,045) survived ≥5 years. Among them, 1,227 had underwent surgery, and 708 did not receive any surgical intervention. Among patients who were non-surgically managed, the factor most strongly associated with good prognosis (overall survival ≥5 years) in multivariable logistic regression modeling was whether the patient was offered a surgery (odds ratio 2.26; 95% confidence interval 1.4-3.66; $p < 0.001$). Young age, treatment at an academic center, chemotherapy, epithelioid histology, and clinical stage I disease were other characteristics associated with improved survival among non-surgically treated patients. In propensity-matched cohorts, patients receiving chemotherapy and declining surgery (n=116) had nearly identical 5-year overall survival (OS) (16.4%; median OS 22.9 months; IQR 10.8-38.2) as those receiving chemotherapy and surgery (n=232; 16.4% 5y OS; median OS 21.9 months; IQR 11.6-50.9; p=0.77).

Conclusion: NCDB data align with the randomized MARS 2 findings, showing that long-term survival without curative intent surgical resection is possible for some patients with mesothelioma. Notably, over 16% of chemotherapy-treated patients who declined surgery survived ≥5 years after diagnosis. Patients who received chemotherapy and declined surgery had similar survival to those who underwent a recommended surgery. In the non-surgically managed cohort, the strongest predictor of improved survival was whether the patient was offered a surgery, suggesting that patients with already favorable characteristics tend to be cherry-picked for surgery. Methods to identify patients who are most likely to achieve long-term survival based on clinical or biologic features are needed to refine prognostication and guide treatment.

YALE SURGERY RESEARCH DAY 2025

QUALITY IMPROVEMENT ABSTRACTS

COST-EFFECTIVENESS ANALYSIS OF EARLY SURGERY VERSUS PERCUTANEOUS DRAIN PLACEMENT WITH INTERVAL SURGERY FOR COMPLICATED DIVERTICULITIS WITH ABSCESS FORMATION

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Introduction: The optimal timing of non-emergent resection for patients with complicated diverticulitis remains controversial. Early surgery is associated with increased rates of stoma formation and surgical morbidity. In contrast, interval surgery following an image-guided percutaneous drainage strategy, when inflammation has decreased, prolongs disease management and is subject to repeat diverticulitis flares. This study performed a cost-effectiveness analysis of early surgery compared to percutaneous drain placement with interval surgery for diverticulitis with abscess formation.

Methods: A tree-based decision analysis model was constructed for a reference case patient undergoing early surgery versus interval surgery for complicated diverticulitis with abscess formation. Probabilities and utilities (quality-adjusted life years, QALYs) were sourced from secondary literature and Merative MarketScan healthcare claims data (2017-2022). Costs were obtained using Merative MarketScan healthcare claims data. “Early surgery” was defined as a non-emergent sigmoid colectomy performed within 30 days of index admission. “Interval surgery” was defined as a sigmoid colectomy performed over 30 and under 120 days from index admission following a percutaneous drainage procedure. Three surgical procedure types were considered: Hartmann procedure (HP) and primary anastomosis with or without diverting loop ileostomy (PADLI/PA). Outcomes assessed include total discounted economic costs, effectiveness (QALYs), and incremental cost effectiveness ratio (ICER, cost per QALY gained). A probabilistic sensitivity analysis was performed to account for uncertainty.

Results: Early surgery was the more cost-effective strategy. Expected total costs for early surgery were $9,611 less than interval surgery, and early surgery yielded 0.58 more QALYs per patient. This relationship held true for all procedure types, with lower costs and higher QALYs attained for early HP (-$28,996, +0.5 QALYs), early PADLI (-$31,394, +0.90 QALYs), and early PA (-$12,957, +1.05 QALYs) compared to interval surgery. Sensitivity analysis satisfied this conclusion in 97.7% of cases. The threshold QALY decrement from percutaneous drainage to maintain cost-effectiveness favoring the early surgery strategy was as low as 0.032 (out of 1 QALY).

Conclusion: Early surgery was the dominant strategy for surgical management of complicated diverticulitis. The superiority of early surgery was challenged in conditions where temporary percutaneous drain placement did not impact patient quality of life. Therefore, interval surgery may represent the optimal option in patients who have an external strong preference to delay intervention. This threshold for strategy variation emphasizes the importance of shared decision-making with patients around timing of surgery in cases of complicated diverticulitis with abscess formation.