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Alhalabi O, Yadav S and Jaiyesimi IA (2016). "Prescribing patterns of rasburicase and Glucose-6-Phosphate dehydrogenase (G6PD) testing in a large community health system." Journal of Clinical Oncology 34. ePub Ahead of Print.

Full-Text

Department of Internal Medicine

Background: Rasburicase is a recombinant urate-oxidase used in prevention and treatment of tumor lysis syndrome (TLS). Since conversion of uric acid to allantoin leads to the production of hydrogen peroxide as a by-product, Rasburicase is contraindicated in patients with G6PD deficiency. Rasburicase-induced hemolysis occurs in < 1% of recipients. It is recommended that physicians screen for G6PD deficiency in patients at risk prior to administration of Rasburicase. This study assesses adherence to this recommendation and evaluates the incidence of Rasburicase-induced hemolysis. Methods: A retrospective analysis of 361 adult patients who received Rasburicase at Beaumont Health between 2009 and 2015 was conducted. These patients were identified by query of the electronic medication administration record. Cairo-Bishop criteria were used to define TLS. Data on demographics, presence of TLS, G6PD testing and level, and hemolytic reaction post administration was collected. Statistical analysis was performed using RStudio. Chi-square and Wilcoxon rank-sum tests were used to compare categorical and continuous variables, accordingly. Results: Rasburicase was used emergently for treatment of TLS in only 94 (26%) patients. On average, G6PD test resulted 35.6 hours after administration of Rasburicase. 59 (16%) of the recipients were identified as high risk race/ethnicity for G6PD deficiency. African Americans and Middle Easterns were more likely to be G6PD tested, (OR 2.92, 95% CI 1.33 to 6.01, p = 0.007). However, only 12 (20.3%) of these at-risk patients were tested. 5 (13.5%) of G6PD tested subjects were found to be deficient. Of these, 4 (80%) developed hemolysis post Rasburicase administration. Conclusions: Only a minority of at-risk patients were tested for G6PD deficiency prior to receiving Rasburicase. Perhaps, the delayed G6PD result timing or the urgency in giving Rasburicase lead to this shortcoming. Nonetheless, in light of the relatively common incidence of G6PD deficiency among tested individuals, further interventions beside blackbox warning are needed to improve adherence. Knowing the G6PD status is important to predict and promptly manage adverse events.


Full-Text

Department of Internal Medicine

Objectives: The number of operations performed per surgeon is thought to determine the quality of carotid endarterectomy (CEA) surgery. The advent of carotid artery stenting (CAS) threatens to reduce the volume of CEA. This paper assesses CEA and the effects of the introduction of CAS service on outcomes. Design: Retrospective cohort study. Methods: Clinical data and results of CEA were reviewed retrospectively for the treatment of carotid stenosis, between January 1988 and December 2010. CEA patients were grouped into those treated before and after the introduction of CAS to our hospital in 2001. Results: 757 patients underwent a CEA between 1988 and 2010. The periprocedural stroke rate prior to the introduction of CAS was 4.9%, and 3.3% after stent introduction in 2001. In this latter period, 85.5% had symptomatic stenosis which suggests that the patients were not low risk. The major adverse event rate (inclusive of death and myocardial infarction) post introduction of CAS from 2001 to 2010 was 4.1%. There was no correlation between post-operative stroke/MAE and procedure volume, despite the trend of decreasing CEA numbers over time. Conclusion: The introduction of carotid artery stenting has led to a decrease in carotid endarterectomy volume. However, outcomes in our high risk patient population are acceptable. Therefore, CEA remains the procedure of choice for carotid artery revascularization.


Full-Text

Department of Diagnostic Radiology and Molecular Imaging

Purpose: The primary objective of this study was to determine the clinical outcomes in cases of appendix nonvisualization with MRI in pregnant patients with suspected appendicitis and the implications of appendix nonvisualization for excluding appendicitis. Methods: Fifty-eight pregnant patients with suspected appendicitis evaluated with MRI at three centers from a single institution were retrospectively reviewed by three radiologists with varying levels of abdominal imaging experience. All scans were performed on a 1.5-Tesla Siemens unit. Cases were evaluated for diagnostic quality, visualization of the appendix, presence of appendicitis, and alternate diagnoses. Clinical outcomes were gathered from the electronic medical record. Results: Of the 58 patients who underwent MRI for suspected appendicitis, 50 cases were considered adequate
diagnostic quality by all three radiologists. The rate of appendix visualization among the three radiologists ranged from 60 to 76% (p = 0.44). The appendix was nonvisualized by at least one of the three radiologists in 25 cases (50%). Of these, none had a final diagnosis of appendicitis including one patient who underwent appendectomy. MRI suggested an alternate diagnosis in 6 (24%) patients with appendix nonvisualization. For the three reviewers, the agreement level on whether or not the appendix was visualized on the MRI had a Light's kappa value of 0.526, indicating a “moderate” level of agreement (p value < 0.01). Conclusion: Despite only moderate level of interobserver agreement for appendix visualization, appendix nonvisualization on MRI in pregnant patients with suspected appendicitis confers a significant reduction in the risk of appendicitis compared to all comers as long as the study is adequate diagnostic quality and there are no secondary signs of appendicitis present. © 2016 Springer Science+Business Media New York


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Department of Biomedical Sciences (OU)


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Department of Biomedical Sciences (OU)

Online versions of traditional face-to-face (F2F) courses at post-secondary institutions have become prevalent due to increased enrollment in undergraduate programs. While many studies assess the impact of online delivery formats on student outcomes, fewer examine how teaching online affects instructors. An online section of a traditional F2F undergraduate anatomy course with a prosection laboratory commenced in 2012-13 at Western University Canada. Lectures for F2F students (N=365) were broadcast in both live and archived format to online students (N=40) using virtual classroom software. Laboratories were delivered online by a teaching assistant who manipulated 3D computer models in the virtual classroom environment. An exploratory sequential mixed methods approach was undertaken to determine the most important deciding factors that drive students' preferences for a given format and then to generate theory on the strengths and weaknesses of the online format. Students (20 online; 310 F2F) volunteered to participate in a crossover period of one week to expose them to the course section in which they were not originally registered. Open ended interviews (20 online; 20 F2F) and quantitative surveys (270 F2F) were conducted following a crossover. Students valued pace control, schedule, and location flexibility of learning from archived materials and being assessed online. In the online laboratory they had difficulty using the 3D models and preferred the unique and hands-on experiences of cadaveric specimens. The F2F environment was conducive to learning in both lecture and laboratory because students felt more engaged by instructors in person and were less distracted by their surroundings. These results suggest the need to improve the online experience by increasing the quality of student-instructor communication and in turn student-content interaction with the 3D models. © 2016 American Association of Anatomists.
understanding.


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Department of Obstetrics and Gynecology

OUWB Medical Student Author

Objective: Our primary objective was to apply metabolomic pathway analysis of first trimester maternal serum to provide an insight into the pathogenesis of late-onset preeclampsia (late-PE) and thereby identify plausible therapeutic targets for PE. Methods: NMR-based metabolomics analysis was performed on 29 cases of late-PE and 55 unaffected controls. In order to achieve sufficient statistical power to perform the pathway analysis, these cases were combined with a group of previously analyzed specimens, 30 late-PE cases and 60 unaffected controls. Specimens from both groups of cases and controls were collected in the same clinical centers during the same time period. In addition, NMR analyses were performed in the same lab and using the same techniques. Results: We identified abnormalities in branch chain amino acids (valine, leucine and isoleucine) and propanoate, glycolysis, gluconeogenesis and ketone body metabolic pathways. The results suggest insulin resistance and metabolic syndrome, mitochondrial dysfunction and disturbance of energy metabolism, oxidative stress and lipid dysfunction in the pathogenesis of late PE and suggest a potential role for agents that reduce insulin resistance in PE. Conclusions: Branched chain amino acids are known markers of insulin resistance and strongly predict future diabetes development. The analysis provides independent evidence linking insulin resistance and late-PE and suggests a potentially important therapeutic role for pharmacologic agents that reduce insulin resistance for late-PE.


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Department of Emergency Medicine


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Department of Emergency Medicine

Objective: This study analyzed outcomes associated with nurse-performed ultrasound (US)-guided intravenous (IV) placement compared to standard of care (SOC) palpation IV technique on poor vascular access patients. Methods: This was a randomized, prospective single-site study. Phase 1 involved education/training of a cohort of nurses to perform US-guided IVs. This consisted of a didactic module and hands-on requirement of 10 proctored functional IVs on live subjects. Phase 2 involved patient enrollment, emergency department patients meeting strict criteria of poor access were randomized to US-guided or SOC palpation arm. A functional IV placement was considered successful. Unsuccessful placement implied the study nurse failed, and a rescue IV was attempted. Time to IV placement was the total time required to obtain a functional IV and, if needed, a rescue IV. Results: A total of 124 subjects were enrolled; 63 were randomized to the US-guided arm, and 61 were randomized into the SOC arm; 2 patients were excluded, leaving 59 patients. Success rate was 76% for the US-guided arm and 56% for the SOC arm (P = .02). Compared to the SOC arm, the odds ratio for success for the US-guided arm was 2.52 (95% confidence interval, 1.09-5.92). The mean time to IV placement for the US-guided arm was 15.8 and 20.7 minutes for the SOC arm (P = .75). Conclusion: In difficult access patients, nurses were more successful in obtaining IV access using US guidance than palpation SOC technique. Lengthier placement times were observed more frequently when the SOC IV technique was used.


Full-Text

Department of Surgery

BACKGROUND: The optimal management of type B aortic dissection (TBAD) remains controversial in the era of endovascular therapies. This study reports the outcomes and complication rates of different treatment paradigms for TBAD. METHODS: A retrospective review was undertaken of all patients with TBAD from June 2006 to June 2012. Demographics, hospital course, and follow-up visits were analyzed. Patients who underwent surgical interventions were compared to those with medical therapy. Survival rates and predictors of outcome were determined using the Kaplan-Meier method with Cox proportional hazards. RESULTS: Of 261 consecutive
patients who were hospitalized during this period with a confirmed thoracic dissection, 134 (51%) had TBAD. Sixty-two (46%) were women, and the mean age was 66.4 +/- 14.9. Median follow-up was 22.4 (0, 184) months. Thirty-five patients underwent surgical intervention with 20 thoracic endovascular aortic repair (TEVAR) and open surgery in 15. The overall 30-day mortality was 7%, and cumulative survival rates at 1, 3, and 5 years were 85% (95% confidence interval [CI], 79-91), 68% (95% CI, 59-78), and 57% (95% CI, 47-69) with no difference between medical versus surgical groups (P = 0.8) and TEVAR versus open surgery group (P = 1.0). Sixty-six (50%) patients developed aneurysmal expansion, which required surgical intervention in 26 (hazard ratios [HR], 0.99; P = 0.96). Mal perfusion and rupture only occurred in 5 (HR, 1.57; P = 0.54) and 5 (HR, 3.64; P = 0.01) patients, respectively. Multivariate analysis for overall survival found renal insufficiency (HR, 2.6; P = 0.004) and age (HR, 1.06; P < 0.0001) and rupture (HR 3.3, P = 0.04) were independent predictors of mortality. Intramural hematoma was not a significant predictor of survival (HR, 0.49; P = 0.11). CONCLUSIONS: Medical therapy remains the mainstay of treating TBAD with low morbidity. Surgical interventions are indicated in patients with malperfusion or aneurysmal expansion with comparable survival rates.


on univariate analysis. Patients with both high CD44 and c-MET expression had a poor prognosis with a 2-year DFS of 30% compared to 70% in the rest of the cohort (P = 0.003). On multivariable analysis, after adjusting for site, T-stage, smoking history, and EGFR status, high c-MET (P = 0.039) and negative p16 status (P = 0.034) predicted for worse DFS, while high CD44 expression did not (P = 0.43). Conclusions: High CD44 expression is associated with high c-MET expression, p16-negative tumors, and EGFR-positive tumors. The combination of these markers predicts for poor prognosis in HNSCC patients treated with chemoradiation. © 2016 John Wiley & Sons A/S.


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Department of Radiation Oncology


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Department of Pathology

Tuberous sclerosis complex (TSC) results from mutation of TSC1 or TSC2 that encode for hamartin and tuberin. It affects the kidneys often in advance of extra-renal stigmata. We studied 14 TSC cases, and 4 possible TSC cases with multiple angiomyolipomas (AMLs) for hamartin and tuberin protein expression to determine if the staining profile could predict mutation status or likelihood of TSC with renal-limited disease. The 18 cases included 15 nephrectomies and 1 section of 6 TSC-associated renal cell carcinomas (RCC). Controls included the non-neoplastic kidney in 5 tumor nephrectomies, 4 sporadic cases of AML and 6 clear cell RCCs. In the 14 TSC cases, 9 had AMLs, 9 had RCCs, 5 had polycystic kidney disease and 8 had eosinophilic cysts (EC) lined by large eosinophilic cells. The controls and study cases showed luminal staining of proximal tubules (PT) and peripheral membrane staining in distal tubules/collecting ducts for hamartin and cytoplasmic staining for tuberin. Eosinophilic cysts had a luminal PT-like stain with hamartin and a cytoplasmic reaction for tuberin. Hamartin stained myoid cells in all AMLs. Tuberin was negative in all but 1 AML, an epitheloid AML. All but 1 RCC were positive for tuberin; 13 RCCs (7 TSC/6 non-TSC) were negative for hamartin and 4 showed a weak reaction. We conclude that the ECs of TSC are proximal tubule-derived. The hamartin and tuberin staining profiles of AMLs and most RCCs are reciprocal precluding prediction of the mutation in TSC, and fail to predict if a patient with multifocal AML has TSC.


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EZH2, a Polycomb Repressive Complex 2 (PRC2) component, is required for the maintenance of an epithelial phenotype in ovarian cancer cells. Inhibiting EZH2, by repressing the enhancer of zeste homolog 2 (EZH2), the catalytic subunit of the polycomb repressive complex 2 (PRC2), catalyzes trimethylation of lysine 27 of histone H3 (H3K27me3) to repress gene transcription. Here we report the functional roles of EZH2-catalyzed H3K27me3 during EMT in ovarian cancer (OC) cells. TGF-beta-induced EMT in SKOV3 OC cells was associated with decreased levels of EZH2 and H3K27me3 (P<0.05). These effects were delayed (~72 h relative to EMT initiation) and coincided with increased (>15-fold) expression of EMT-associated transcription factors ZEB2 and SNAI2. EZH2 knockdown (using siRNA) or enzymatic inhibition (by GSK126) induced EMT-like changes in OC cells. The EMT regulator ZEB2 was upregulated in cells treated with either approach. Furthermore, TGF-beta enhanced expression of ZEB2 in EZH2 siRNA- or GSK126-treated cells (P<0.01), suggesting that H3K27me3 plays a role in TGF-beta-stimulated ZEB2 induction. Chromatin immunoprecipitation assays confirmed that TGF-beta treatment decreased binding of EZH2 and H3K27me3 to the ZEB2 promoter (P<0.05). In all, these results demonstrate that EZH2, by repressing ZEB2, is required for the maintenance of an epithelial phenotype in OC cells.

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BACKGROUND: Reported results of ruptured abdominal aortic aneurysm (rAAA) in patients with antecedent endovascular aneurysm repair (EVAR) to those presenting with de novo rupture show a similar or slightly improved outcome. The aim of this study was to compare differences in the presentation and outcomes of rAAA with and without prior EVAR. METHODS: A retrospective review of 121 patients with rAAA, ruptured identified 2 groups. Group A included 17 patients (rAAA n = 17) with antecedent EVAR and group B consisted of 104 patients (rAAA n = 104) with de novo ruptures, from January 2001 to March 2015 in 3 teaching hospitals. Patient characteristics and perioperative variables were compared; Fisher's exact test was used for categorical variables. For continuous variables, Student's t-test and Mann-Whitney U test were used. RESULTS: Both groups were similar in age, gender, the incidence of hypertension, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, and nicotine abuse. Mean time of presentation from EVAR to rupture in group A was 42 +/- 22 months. Mean preoperative transverse or anteroposterior diameter of AAA was 6.6 cm in group A and 7.1 cm in group B. Three patients of 17 (17.6%) in group A were hemodynamically unstable as compared to 47 of 104 patients (45.1%) in group B (P = 0.03). Mean red blood cells, fresh frozen plasma, and platelet transfusion were similar in both groups. Thirty-day mortality was 8 of 17 (44.7%) in group A and 44 of 104 (42.3%) in group B (P = 1.0). Postoperative complications were also similar in both groups except the incidence of postoperative respiratory failure was higher in group B (38%) as compared with 11.1% in group A (P = 0.001). CONCLUSIONS: Patients presenting with rAAA with antecedent EVAR are hemodynamically more stable as compared with patients with de novo rupture of AAA. Postoperative respiratory failure is more common in
Purpose: To determine the best predictor of the mid urethral sling outcome we calculated the AUC of ROC curves of preoperative parameters, including Valsalva leak point pressure, maximum urethral closure pressure, urinary NTx (N-telopeptide of crosslinked type I collagen) and plasma vitamin D values (D2, D3 and D2 plus D3).

Materials and Methods: This was an ancillary study of TOMUS (Trial of Mid-urethral Slings) and the ValUE (Value of Urodynamics Evaluation) trial in which subjects underwent mid urethral sling surgery for stress urinary incontinence. Valsalva leak point pressure and maximum urethral closure pressure were measured in 427 subjects, whereas NTx, vitamin D2, vitamin D3 and vitamin D2 plus D3 levels were obtained from 150, 116, 115 and 116 subjects respectively. Outcome success was defined using identical outcome (subjective and objective) variables for all subjects. ROC curves with corresponding AUC values were compared. Results: TOMUS and ValUE subjects were significantly different in age, body mass index, UDI (Urogenital Distress Inventory) scores. TOMUS subjects had a lower surgical success rate compared to ValUE subjects (66.3% vs 76.0%, p = 0.03). The AUC values of Valsalva leak point pressure, maximum urethral closure pressure, NTx, and vitamins D2, D3 and D2 plus D3 were 0.542, 0.561, 0.702, 0.627, 0.645 and 0.640, respectively. The AUC of NTx was significantly higher than the AUCs of Valsalva leak point pressure and maximum urethral closure pressure (p = 0.02 and 0.03, respectively). Conclusions: Urinary NTx was the best predictor of the mid urethral sling outcome. This test is not only noninvasive, it is also modifiable. Finding ideal modifiable risk factors prior to mid urethral sling surgery should be subject to future investigations.


technique to quantify the apparent binding of CD20 and R. As the GLU residue pKa of CN-14 increased, the affinity of the SAM to Rituximab increased while the selectivity decreased. This was attributed to the weakening of the salt bridge between the CN-14 ARG-10 and GLU-13 at higher pKa values for GLU-13. Conclusions: Interaction of CD20 antigens with antibodies will help physicians to determine the clinical efficacy and resistance mechanisms to antibodies like R. QCM is low cost, highly sensitive, fast, synthetic, assay which could be used as a basis for developing a new generation of affinity-based Imunosensor assays. Our study shows that peptide mimotopes have potential benefit in sensor applications as the peptide-peptide interactions in the SAM could be manipulated by the addition of functional groups to the peptide to influence binding of the target protein as well as for surface immobilization via SAM.


Department of Orthopedic Surgery

Background: Stemmed humeral components have been used since the 1950s; canal-sparing (also known as stemless) humeral components became commercially available in Europe in 2004. The Simpliciti total shoulder system (Wright Medical, formerly Tornier) is a press-fit, porous-coated, canal-sparing humeral implant that relies on metaphyseal fixation only. This prospective, single-arm, multicenter study was performed to evaluate the two-year clinical and radiographic results of the Simpliciti prosthesis in the U.S. Methods: One hundred and fifty-seven patients with glenohumeral arthritis were enrolled at fourteen U.S. sites between July 2011 and November 2012 in a U.S. Food and Drug Administration (FDA) Investigational Device Exemption (IDE)-approved protocol. Their range of motion, strength, pain level, Constant score, Simple Shoulder Test (SST) score, and American Shoulder and Elbow Surgeons (ASES) score were compared between the preoperative and two-year postoperative evaluations. Statistical analyses were performed with the Student t test with 95% confidence intervals. Radiographic evaluation was performed at two weeks and one and two years postoperatively. Results: One hundred and forty-nine of the 157 patients were followed for a minimum of two years. The mean age and sex-adjusted Constant, SST, and ASES scores improved from 56% preoperatively to 104% at two years (p < 0.0001), from 4 points preoperatively to 11 points at two years (p < 0.0001), and from 38 points preoperatively to 92 points at two years (p < 0.0001), respectively. The mean forward elevation improved from 103° ± 27° to 147° ± 24° (p < 0.0001) and the mean external rotation, from 31° ± 20° to 56° ± 15° (p < 0.0001). The mean strength in elevation, as recorded with a dynamometer, improved from 12.5 to 15.7 lb (5.7 to 7.1 kg) (p < 0.0001), and the mean pain level, as measured with a visual analog scale, decreased from 5.9 to 0.5 (p < 0.0001). There were three postoperative complications that resulted in revision surgery: infection, glenoid component loosening, and failure of a subscapularis repair. There was no evidence of migration, subsidence, osteolysis, or loosening of the humeral components or surviving glenoid component. Conclusions: The study demonstrated good results at a minimum of two years following use of the Simpliciti canal-sparing humeral component. Clinical results including the range of motion and the Constant, SST, and ASES scores improved significantly, and radiographic analysis showed no signs of loosening, osteolysis, or subsidence of the humeral components or surviving glenoid component. Level Of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.


Department of Diagnostic Radiology and Molecular Imaging

We will review and illustrate the multiple advantages of ultrasound as an image guidance tool, including real-time vessel visualization, multiplanar capability, portability/availability, and decreased procedure time and cost. We will demonstrate the unique advantages of the use of this imaging modality in the biopsy of small parenchymal lesions particularly those that are not visible with unenhanced computed tomography (CT) or not persistently visible with contrast-enhanced CT or those lesions not readily accessible by CT guidance, the use of direct probe compression to displace bowel away from biopsy targets, the use of direct probe compression to staunch intraprocedural bleeding observed with real-time visualization to minimize postprocedural bleeding complications, and the ability to biopsy masses in pediatric patients as a function of the inherent lack of ionizing radiation. Finally, we will review and illustrate how the use of preprocedural lesion characterization with ultrasound at times can serve as a problem-solving tool providing an alternative and reasonably confident diagnosis and thus avoiding unnecessary procedures and associated potential risks. © 2016 Wolters Kluwer Health, Inc.
Within this millennium there has been resurgence in funding and research dealing with animal models of radiation-induced lung injury to identify and establish predictive biomarkers and effective mitigating agents that are applicable to humans. Most have been performed on mice but there needs to be assurance that the emphasis on such models is not misplaced. We therefore considered it timely to perform a comprehensive appraisal of the literature dealing with radiation lung injury of mice and to critically evaluate the validity and clinical relevance of the research. A total of 357 research papers covering the period of 1970-2015 were extensively reviewed. Whole thorax irradiation (WTI) has become the most common treatment for studying lung injury in mice and distinct trends were seen with regard to the murine strain, radiation dose, intended pathology investigated, length of study, and assays. Recently, the C57BL/6 strain has been increasingly used in the majority of these studies with the notion that they are susceptible to pulmonary fibrosis. Nonetheless, many of these investigations depend on animal survival as the primary end point and neglect the importance of radiation pneumonitis and the anomaly of lethal pleural effusions. A relatively large variation in survival times of C57BL/6 mice is also seen among different institutions pointing to the need for standardization of radiation treatments and environmental conditions. An analysis of mitigating drug treatments is complicated by the fact that the majority of studies are limited to the C57BL/6 strain with a premature termination of the experiments and do not establish whether the treatment actually prevents or simply delays the progression of radiation injury. This survey of the literature has pointed to several improvements that need to be considered in establishing a reliable preclinical murine model of radiation lung injury. The lethality end point should also be used cautiously and with greater emphasis on other assays such as non-invasive lung functional and imaging monitoring in order to quantify specific pulmonary injury that can be better extrapolated to radiation toxicity encountered in our own species. © 2016 USCAP, Inc All rights reserved.


OUWB Medical Student Author

Birth plans were developed with the intention of enhancing women’s prepared decision-making in the labor and delivery process and to offer obstetric care providers with important details about those decisions. Through the use of birth plans, women can reflect on their values and choices regarding what care practices and interventions they do and do not want in birth, and they can communicate these values in advance to their care providers. However, birth plans are often ineffective at accomplishing their goals for a number of reasons. They may reflect outdated concerns about routine practices or overly emphasize minor matters. Many popular pregnancy websites offer birth plans that utilize checklist formats, and women who use these are not counseled about which options may require or preclude other options. Some women may have inappropriately rosy expectations of how their labor and delivery processes will progress or have received poor advice. The use of a birth plan may invoke hostility from hospital staff, who may disregard the plans and look down upon the women who make them. An alternative approach to the use of birth plans to enhance women’s participation and informed consent in the birth process is the birth partnership, in which women and their obstetric care providers take time to thoroughly discuss the choices to be made in birth in advance in order to have those choices best reflect the values of the women giving birth. Meeting to discuss values and choices prior to labor offers opportunity for mutual education between provider and patient about the choices to be made and the values that inform those choices. Effective communication and working to build mutual trust can serve as preventive measures to avoid many conflicts that arise in the birth process.


OBJECTIVE: To evaluate the hospital-realized cost difference between transvaginal mesh prolapse repair and robot-assisted sacrocolpopexy. METHODS: Consecutive transvaginal mesh prolapse surgery and robot-assisted sacrocolpopexy cases from January 2012 to December 2013 were evaluated. Patient clinical and operative data were recorded. The total institutional costs (direct and indirect) for each procedure were obtained and subcategorized by area. Independent sample t tests and chi-squared analysis were performed. RESULTS: One hundred twenty women underwent transvaginal mesh repair whereas 106 underwent robotic sacrocolpopexy. Body mass index was similar between groups (28.1 vs 27.5) as was midurethral sling placement (50% vs 59%). Robotic patients were younger (61 years vs 67 years, P < .001) and more likely to undergo concomitant hysterectomy (58.5% vs 26.7%). There were similar rates for additional compartment repairs. Amortized costs for robotic purchase and maintenance were included with all depreciated equipment and realized by all patients undergoing surgery. Overall mean robotic operative time was longer with and without hysterectomy (279 minutes vs 174 minutes, P < .001 and 201 minutes vs 91 minutes, P < .001). Mean total costs were higher with robotic technique ($9675 vs $6718, P < .001), primarily driven by anesthesia ($1141 vs $675, P < .001), and operative ($6883 vs $4487, P < .001) costs. No differences for total costs were seen in laboratory fees, recovery room, or inpatient nursing. CONCLUSION: Transvaginal prolapse repair is less costly than robotic sacrocolpopexy. Length of surgery and additional robotic supplies drive the majority of increased operative costs. Costs attributed to robotic purchase and maintenance do not uniquely factor into the procedure costs.

Skin and corneal wounds in diabetics are a major healthcare burden. MicroRNAs are small, non-coding RNAs that post-transcriptionally regulate the expression of protein-coding genes. Studies have identified microRNAs involved in all phases of wound healing. The dysregulation of microRNAs can contribute to impaired or delayed skin and corneal wound healing in diabetics. Here, we present a comprehensive review of the literature involving microRNAs in diabetic skin and corneal wound healing as well as those serving as potential biomarkers for diabetic wound healing. © 2016 Bentham Science Publishers.

Purpose: To assess the prevalence, awareness, and quality of life (QOL) impact of symptoms suggestive of underactive bladder (UAB) in the USA. Methods: A thirteen-item paper survey was mailed to 25,000 individuals 60 years or older living in the USA. It aimed to collect information relating to demographics, familiarity with UAB, patient urinary symptoms, and QOL concerns. Results: Nine hundred and seventy-seven survey participants were stratified into four groups based on the number of UAB symptoms (straining, retention, and difficulty emptying) present: zero, one, two, and three. As the number of reported UAB symptoms increased, there was an increase prevalence in nocturia, urge, and urinary frequency (p < 0.0001). Increased UAB symptoms were associated with an increased prevalence of concerns related to urgency, urge incontinence, nocturia, and overall urinary status (p < 0.0001). Urology visits were most common in individuals who reported the most UAB symptoms (p < 0.0001); however, there was no difference among groups with regard to UAB awareness. Women were less likely to report any UAB symptoms (p < 0.0001), symptoms of urge (p = 0.001), retention (p = 0.002), difficulty emptying their bladder (p < 0.0001), a history of catheter use for retention (P = 0.002), and urology visits in the past 3 years (p < 0.0001). This study is limited in its inability to differentiate...
UAB from disorders that may mimic UAB clinically, based on the survey questions asked. Conclusions: Underactive bladder symptoms are common and can have a significant impact on one's QOL, although awareness is still lacking among potentially affected individuals. More must be done to allow one to better differentiate between UAB and conditions that are clinically similar.
Department of Pediatrics

The lytrophic herpesviruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus 6B (HHV-6B) can reactivate and cause disease in organ transplant recipients; the contributions of HHV-6A and HHV-7 to disease are less certain. Less is known about their pathogenic roles in children undergoing treatment for malignancies. Children with newly diagnosed cancer were followed for 24 months. Clinical information and blood samples were collected during routine visits and during acute visits for fever or possible viral infections. Lymphotrophic herpesvirus DNA in blood was measured by polymerase chain reaction (PCR). Although HHV-6B DNA was detected at least once in about half of the patients; the other viruses were seldom detected. There was no association between HHV-6B detection and individual acute clinical events, however, HHV-6B detection was more common in children who experienced more frequent acute clinical events. In children being treated for various malignancies, HHV-6B detection was common, but was not associated with individual events of acute illness. Thus, if HHV-6B is not assessed longitudinally, clinical events may be misattributed to the virus. The elevated frequency of detection of HHV-6B in sicker children is consistent with prior reports of its detection during apparently unrelated acute clinical events.

Department of Biomedical Sciences (OU)

BACKGROUND: Obtaining high-quality images of cellular structures via immunofluorescence staining is critical for cellular localization studies. Often, these studies cannot be performed in parallel with certain oncology, virology, pharmacokinetic, and drug absorption studies due to model system technicalities requiring the cells to be cultured on porous membranes rather than glass or plastic. MATERIAL AND METHODS: Here, we report a method of immunofluorescent staining of cells cultured on permeable membranes. RESULTS: As proof of principle, HeLa cells grown on Transwell(R) membrane supports were stained with fluorescently labeled antibodies using this modified immunofluorescence staining method and visualized by fluorescent microscopy. CONCLUSIONS: This protocol is a convenient alternative to staining cells on glass coverslips, thereby expanding the scope and applications of this important research tool.

Department of Internal Medicine

BACKGROUND: Left ventricular (LV) volumetric and functional parameters measured with cardiac computed tomography (cardiac CT) augment risk prediction and discrimination for future mortality. Gender- and age-specific standard values for LV dimensions and systolic function obtained by 64-slice cardiac CT are lacking.

METHODS AND RESULTS: 1155 patients from the Coronary CT Angiography Evaluation for Clinical Outcomes: An InteRnational Multicenter registry (54.5% males, mean age 53.1 +/- 12.4 years, range: 18-92 years) without known coronary artery disease (CAD), structural heart disease, diabetes, or hypertension who underwent cardiac CT for various indications were categorized according to age and sex. A cardiac CT data acquisition protocol was used that allowed volumetric measuring of LV function. Image interpretation was performed at each site. Patients with significant CAD (>50% stenosis) on cardiac CT were excluded from the analysis. Overall, mean left ventricular ejection fraction (LVEF) was higher in women when compared with men (66.6 +/- 7.7% vs. 64.6 +/- 8.1%, P < 0.001). This gender-difference in overall LVEF was caused by a significantly higher LVEF in women >/=70 years when compared with men >/=70 years (69.95 +/- 8.9% vs. 65.50 +/- 9.42%, P = 0.004). Accordingly, a significant increase in LVEF was observed with age (P = 0.005 for males and P < 0.001 for females), which was more pronounced in females (5.21%) than in males (2.6%). LV end-diastolic volume decreased in females from 122.48 +/- 27.87 (<40 years) to 95.56 +/- 23.17 (>70 years; P < 0.001) and in males from 155.22 +/- 35.07 (<40 years) to 130.26 +/- 27.18 (>70 years; P < 0.001). CONCLUSION: Our findings indicate that the LV undergoes a lifelong remodelling and highlight the need for age and gender adjusted reference values.

Department of Pediatrics

The lymphotropic herpesviruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus 6B (HHV-6B) can reactivate and cause disease in organ transplant recipients; the contributions of HHV-6A and HHV-7 to disease are less certain. Less is known about their pathogenic roles in children undergoing treatment for malignancies. Children with newly diagnosed cancer were followed for 24 months. Clinical information and blood samples were collected during routine visits and during acute visits for fever or possible viral infections. Lymphotrophic herpesvirus DNA in blood was measured by polymerase chain reaction (PCR). Although HHV-6B DNA was detected at least once in about half of the patients; the other viruses were seldom detected. There was no association between HHV-6B detection and individual acute clinical events, however, HHV-6B detection was more common in children who experienced more frequent acute clinical events. In children being treated for various malignancies, HHV-6B detection was common, but was not associated with individual events of acute illness. Thus, if HHV-6B is not assessed longitudinally, clinical events may be misattributed to the virus. The elevated frequency of detection of HHV-6B in sicker children is consistent with prior reports of its detection during apparently unrelated acute clinical events.


Objectives: To compare the accuracy of two-dimensional ultrasound (2D-US), three-dimensional ultrasound (3D-US) and magnetic resonance imaging (MRI) for the diagnosis of congenital anomalies without prior knowledge of indications and previous imaging findings. Methods: This was a prospective, blinded case-control study comprising women with a singleton pregnancy with fetal congenital abnormalities identified on clinical ultrasound and those with an uncomplicated pregnancy. All women volunteered to undergo 2D-US, 3D-US and MRI, which were performed at one institution. Different examiners at a collaborating institution performed image interpretation. Sensitivity and specificity of the three imaging methods were calculated for individual anomalies, based on postnatal imaging and/or autopsy as the definitive diagnosis. Diagnostic confidence was graded on a four-point Likert scale. Results: A total of 157 singleton pregnancies were enrolled, however nine cases were excluded owing to incomplete outcome, resulting in 148 fetuses (58 cases and 90 controls) included in the final analysis. Among cases, 13 (22.4%) had central nervous system (CNS) anomalies, 40 (69.0%) had non-CNS anomalies and five (8.6%) had both CNS and non-CNS anomalies. The main findings were: (1) MRI was more sensitive than 3D-US for diagnosing CNS anomalies (MRI, 88.9% (16/18) vs 3D-US, 66.7% (12/18) vs 2D-US, 72.2% (13/18); McNemar's test for MRI vs 3D-US: P=0.046); (2) MRI provided additional information affecting prognosis and/or counseling in 22.2% (4/18) of fetuses with CNS anomalies; (3) 2D-US, 3D-US and MRI had similar sensitivity for diagnosing non-CNS anomalies; (4) specificity for all anomalies was highest for 3D-US (MRI, 85.6% (77/90) vs 3D-US, 94.4% (85/90) vs 2D-US, 92.2% (83/90); McNemar's test for MRI vs
3D-US: P=0.03}; and (5) the confidence of MRI for ruling out certain CNS abnormalities (usually questionable for cortical dysplasias or hemorrhage) that were not confirmed after delivery was lower than it was for 2D-US and 3D-US. Conclusions: MRI was more sensitive than ultrasonography and provided additional information that changed prognosis, counseling or management in 22.2% of fetuses with CNS anomalies. False-positive diagnoses for subtle CNS findings were higher with MRI than with ultrasonography. © 2016 ISUOG. Published by John Wiley & Sons Ltd.


Objectives

Objective: Sudden Infant Death Syndrome (SIDS) is defined as the sudden death of an infant <1 year of age that cannot be explained following a thorough investigation. Currently, no reliable clinical biomarkers are available for the prediction of infants who will die of SIDS. Study Design: This study aimed to profile the medulla oblongata from postmortem human brain from SIDS victims (n=16) and compare their profiles with that of age-matched controls (n=7). Results: Using LC-Orbitrap-MS, we detected 12 710 features in electrospray ionization positive (ESI+) mode and 8243 in ESI- mode from polar extracts of brain. Five features acquired in ESI+ mode produced a predictive model for SIDS with an area under the receiver operating characteristic curve (AUC) of 1 (confidence interval (CI): 0.995-1) and a predictive power of 97.4%. Three biomarkers acquired in ESI- mode produced a predictive model with an AUC of 0.956 (CI: 0.767-0.942) and a predictive power of 77.6%. We confidently identified 5 of these features (L(+)-ergothioneine, nicotinic acid, succinic acid, adenosine monophosphate and azelaic acid) and putatively identify another 4 out of the 15 in total. Conclusions: This study underscores the potential value of metabolomics for studying SIDS. Further characterization of the metabolome of postmortem SIDS brains could lead to the identification of potential antemortem biomarkers for novel prevention strategies for SIDS.

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Department of Anesthesiology

[This corrects the article DOI: 10.1186/s13741-016-0029-0.]


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Department of Internal Medicine


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Department of Biomedical Sciences (BHS)

Purpose The pharmacological treatment of acute pain for opioid-tolerant patients requiring high doses of opioids (greater than 500 mg of oral morphine equivalent per day) can be challenging, suboptimal, and is often based on expert opinions and consensus. Methadone is a mu-opioid agonist, antagonist at the N-Methyl-D-aspartate receptor, and inhibits the reuptake of serotonin and norepinephrine. Methadone is indicated for the treatment of moderate to severe pain which is poorly controlled, despite high doses of opioids. The use of methadone may have particular benefits over other opiates, specifically in patients with a significant opioid tolerance or in patients with neuropathic pain. Patients who are poorly responsive to other opiates or have contraindications to treatment with opiates may have improved analgesia with rotation to methadone. Methadone may be useful for patients with a component of neuropathic pain, for patients who have poorly controlled pain despite appropriate use of other opioids (either due to refractory pain or intolerable side effects), or for patients with a true morphine allergy. Due to incomplete cross-tolerance with other opiates, reduction in dose is required when rotating from another opiate. Several published conversions exist for opioid rotation to methadone, making the calculation more challenging. This requires introduction of more clinical experience and judgment. Here, we evaluate the final dose titration (parenteral and oral formulations) required to comfort, compared to empiric published dosing recommendations. Method We have completed a longitudinal case-series of the first 8 adult patients at our institution from July 2015 - July 2016 who required greater than 500 mg of oral morphine equivalents, and were transitioned to IV methadone for acute pain stabilization with...
subsequent conversion to oral methadone for chronic pain management by the interdisciplinary palliative care service. Outcome measures included total daily dose of oral morphine equivalent required at the time of conversion, initial and final IV methadone regimen, initial and final oral methadone regimen, pertinent drug-drug interactions, EKG monitoring, and self-reported pain scores (numeric rating scale). Final titrated parenteral and oral dose required for pain stabilization will be compared to the empiric dose recommendations from the consensus guideline on parenteral methadone use in pain and palliative care. Results Data collection and analysis are currently being conducted; final results and conclusions will be presented at the 2016 PAINWeek Conference. Conclusions Parenteral methadone dosing guidelines were developed and successfully implemented at a large, tertiary, academic hospital. The mechanisms of action for methadone as compared to traditional opioids provide a unique medical treatment for patients with high opioid-requirements not reaching their therapeutic goal. The pharmacokinetic profile, including variations between oral and parenteral formulations, present significant challenges to prescribers in providing this effective therapy. Supervision, experience, and teamwork make the use of this medication a powerful tool in providing relief from uncontrolled pain for patients that may not otherwise find comfort.


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Department of Anesthesiology

AIM: To compare the ease-of-care (EOC) examining time efficiency, convenience and satisfaction of fentanyl iontophoretic transdermal system ([ITS] IONSYS(R)) and morphine intravenous patient-controlled analgesia (iv. PCA) in postoperative pain management using a validated physical therapist (PT) EOC questionnaire.

MATERIALS & METHODS: This meta-analysis assessed EOC of fentanyl ITS versus morphine iv. PCA using data from two randomized, active-comparator studies (fentanyl ITS: n = 720 and morphine iv. PCA: n = 739) which used the PT EOC Questionnaire (22 items grouped into three subscales; time efficiency, convenience and satisfaction). Each item was scored on a 6-point Likert scale. For time efficiency, PT whose average scores were \(< = 2\) on all items of the time efficiency and convenience subscales or \(>/=4\) on both satisfaction items were considered responders. RESULTS: There were EOC questionnaires from 264 (fentanyl ITS) and 254 (morphine iv. PCA) PTs. There were significantly greater proportions of PTs classified as responders for fentanyl ITS than morphine iv. PCA for overall EOC (81.0 vs 55.7%, respectively), time efficiency (83.1 vs 59.5%, respectively), convenience (87.4 vs 72.0%, respectively) and satisfaction (51.9 vs 30.0%, respectively), all \(p < 0.0001\). CONCLUSION: In this meta-analysis, fentanyl ITS is associated with a superior EOC profile (overall, time efficiency, convenience and satisfaction) from the PTs’ perspective when compared with morphine iv. PCA.


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OUWB Medical Student Author


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Department of Radiation Oncology
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Department of Orthopedic Surgery

Management of the unstable shoulder after a failed stabilization procedure can be difficult and challenging. Detailed understanding of the native shoulder anatomy, including its static and dynamic restraints, is necessary for determining the patient’s primary pathology. In addition, evaluation of the patient's history, physical exam, and imaging is important for identifying the cause for failure after the initial procedure. Common mistakes include under-appreciation of bony defects, failure to recognize capsular laxity, technical errors, and missed
associated pathology. Many potential treatment options exist for revision surgery, including open or arthroscopic Bankart repair, bony augmentation procedures, and management of Hill Sachs defects. The aim of this narrative review is to discuss in-depth the common risk factors for post-surgical failure, components for appropriate evaluation, and the different surgical options available for revision stabilization. Level of evidence Level V.


Request Form


Inherited arrhythmia syndromes are a known, albeit rare, cause of sudden cardiac arrest which may present with characteristic electrocardiogram changes in patients with structurally normal heart. There are a variety of distinct arrhythmogenic syndromes that arise from mutations in voltage gated sodium channels, resulting in either gain or loss of function. We describe a patient with a primary inherited arrhythmia syndrome which presented as sudden cardiac arrest. Further workup revealed that her arrest was due to a combination of Brugada syndrome and Long QT3 syndrome secondary to a deleterious mutation of voltage-gated, sodium channel, type V alpha subunit (SCN5A Thr1709Met).
Background: Preprocedure systemic antibiotic prophylaxis reduces infections in patients undergoing cardiac implantable electronic devices (CIEDs) implantations. Whether pocket irrigation with antibiotic solution offers any advantage over saline solution in CIED implantation is unknown. Methods: Records from 327 consecutive patients who underwent CIED implantation by three operators from February 2011 to January 2014 were reviewed. From February 2011 to January 2012, the antibiotic solution was used for pocket irrigation; from February 2012 to January 2014, saline solution was used. All patients received preprocedural IV antibiotics. Baseline demographics, comorbidities, lab data, and occurrence of any pocket infection postimplant were collected. Results: There were 118 and 209 patients in the antibiotic solution and saline solution group, respectively. A total of four (1.2%) patients had CIED infection: two in the antibiotic solution group and two in the saline solution group. Median time to infection from implant date was 81.5 ± 35 days. Two patients (50%) had infection after first device implantation. Of the four patients, one had positive blood culture, three had positive pocket cultures, one had lead vegetation, one underwent pocket exploration, and all of them had devices/leads extracted, with reimplantation on the contralateral side. No mortality was observed due to infectious complications. Conclusion: When compared to pocket irrigation in the antibiotic solution group, the saline solution group was not associated with increased incidence of infectious complications after CIED implantation. The use of saline solution pocket irrigation alone may be used in CIED pocket irrigation periprocedurally. Further evaluation in larger randomized trials is needed. © 2016 Wiley Periodicals, Inc.


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Department of Emergency Medicine

Introduction: A motor vehicle collision (MVC) is one of the most common life-threatening events experienced by individuals living in the USA. While most individuals recover following MVC, a significant proportion of individuals develop adverse posttraumatic sequelae such as post-traumatic stress disorder or persistent musculoskeletal pain. Adverse post-traumatic sequelae are common, morbid and costly public health problems in the USA and other industrialised countries. The pathogenesis of these disorders following MVC remains poorly understood. In the USA, available data suggest that African-Americans experience an increased burden of adverse post-traumatic sequelae after MVC compared to European Americans, but to date no studies examining the pathogenesis of these disorders among African-Americans experiencing MVC have been performed. Methods and analysis: The African-American CRASH (AA CRASH) study is an NIH-funded, multicentre, prospective study that enrols African-Americans (n=900) who present to the emergency department (ED) within 24 hours of MVC. Participants are enrolled at 13 ED sites in the USA. Individuals who are admitted to the hospital or who report a fracture or tissue injury are excluded. Participants complete a detailed ED interview that includes an assessment of crash history, current post-traumatic symptoms and health status prior to the MVC. Blood samples are also collected in the ED using PAXgene DNA and PAXgene RNA tubes. Serial mixed-mode assessments 6 weeks, 6 months and 1 year after MVC include an assessment of adverse sequelae, general health status and health service utilisation. The results from this study will provide insights into the incidence and pathogenesis of persistent pain and other post-traumatic sequelae in African-Americans experiencing MVC. Ethics and dissemination: AA CRASH has ethics approval in the USA, and the results will be published in a peer-reviewed journal.

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Department of Emergency Medicine

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Department of Radiation Oncology

Purpose: Inaccurate density information may introduce dose calculation errors when inhomogeneity correction is applied. The aim of the present study was to examine the effect of density variation on photon dose calculation accuracy using the convolution/superposition (CS) algorithm with the focus on newer treatment technologies including intensity modulated radiotherapy, volumetric modulated arc radiotherapy, and stereotactic body radiotherapy (SBRT). Methods: Calculations were first performed using simple inhomogeneity phantom models and patient plans to determine clinically relevant tolerance levels for different tissue types. The clinical validity of these tolerance levels was then demonstrated by evaluating their dosimetric impact on clinical treatment plans. Results: For soft tissue and bone, the tolerance levels determined from this study appear to be consistent with the values previously calculated using simpler inhomogeneity correction methods. However, the tolerance level for low density lung tissue has been found to be much smaller than what previous studies had reported. The results from this study also suggest that if density variation is restricted within ±0.02, ±0.03, and ±0.10 g/cm³ for lung, soft tissue, and bone, respectively, the resulting dose error in target volumes can be limited to <2% for most clinical cases and <3% for more challenging lung SBRT cases. When the same amount of density variation is introduced, MC algorithm yields ~0.3%-0.9% and ~0.8%-1.2% smaller dose errors for the target and organs-at-risk as compared to CS. Conclusions: It is important to include lung substitute material into the periodic quality assurance of CT simulators and treatment planning systems. This study suggests that the tolerance value of CT number for lung material is ~±20 HU in order to keep the associated dose uncertainty at 2%-3% or less. Further studies with larger number of lung cases are warranted to validate this new tolerance value before it can be applied to clinical practice.


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Department of Surgery


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Department of Biomedical Sciences (BHS)

Purpose. Results of the MENTORED QUALITY IMPROVEMENT IMPACT PROGRAM SM [MQIIP] on Ensuring Insulin Pen Safety in Hospitals, which was part of an ASHP educational initiative aimed at ensuring the safe use of insulin pens in hospitals, are described. Methods. During this ASHP initiative, which also included continued educational activities and Web-based resources, distance mentoring by pharmacists with expertise in the safe use of insulin pens was provided to interprofessional teams at 14 hospitals between September 2014 and May 2015. The results of baseline assessments of nursing staff knowledge of insulin pen use, insulin pen storage and labeling audits, and insulin pen injection observations conducted in September and October 2014 were used as the basis for insulin pen quality-improvement plans. Postintervention data were collected in April and May 2015. Results. Compared with the baseline period, significant improvement in nurses’ knowledge of insulin pen use, insulin pen labeling and storage, and insulin pen administration were observed in the postintervention period despite the relatively short time frame for implementation of quality-improvement plans. Program participants are committed to sustaining any improvements achieved during the program. The outcome measures described in this report could be adapted by other health systems to identify opportunities to improve the safety of insulin pen use. Conclusion. Focused attention on insulin pen safety through an interprofessional team approach during the MQIIP enabled participating sites to detect potential safety issues based on collected data, develop target process changes, document improvements, and identify areas requiring further intervention. A sustained organizational commitment is required to ensure the safe use of insulin pen devices in hospitals.


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Department of Internal Medicine

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**Department of Anesthesiology**

Purpose: Venous thromboembolism (VTE) is common in cancer patients. Evidence has suggested that low molecular weight heparin (LMWH) might improve survival in patients with cancer by preventing both VTE and the progression of metastases. No trial in a single cancer type has been powered to demonstrate a clinically significant survival difference. The aim of this trial was to investigate this question in patients with lung cancer.

Patients and Methods: We conducted a multicenter, open-label, randomized trial to evaluate the addition of a primary prophylactic dose of LMWH for 24 weeks to standard treatment in patients with newly diagnosed lung cancer of any stage and histology. The primary outcome was 1-year survival. Secondary outcomes included metastasis-free survival, VTE-free survival, toxicity, and quality of life. Results: For this trial, 2,202 patients were randomly assigned to the two treatment arms over 4 years. The trial did not reach its intended number of events for the primary analysis (2,047 deaths), and data were analyzed after 2,013 deaths after discussion with the independent data monitoring committee. There was no evidence of a difference in overall or metastasis-free survival between the two arms (hazard ratio [HR], 1.01; 95% CI, 0.93 to 1.10; P = .814; and HR, 0.99; 95% CI, 0.91 to 1.08; P = .864, respectively). There was a reduction in the risk of VTE from 9.7% to 5.5% (HR, 0.57; 95% CI, 0.42 to 0.79; P = .001) in the LMWH arm and no difference in major bleeding events but evidence of an increase in the composite of major and clinically relevant nonmajor bleeding in the LMWH arm. Conclusion: LMWH did not improve overall survival in the patients with lung cancer in this trial. A significant reduction in VTE is associated with an increase in clinically relevant nonmajor bleeding. Strategies to target those at greatest risk of VTE are warranted.


**Full-Text**

**Department of Orthopedic Surgery**

**OBJECTIVE:** Post-traumatic osteoarthritis (PTOA) is commonly studied using animal models. Surgical ACL transection is an established model, but noninvasive models may mimic human injury more closely. The purpose of this study was to quantify and compare changes in 3D articular cartilage (AC) morphology following noninvasive ACL rupture and surgical ACL transection.

**METHODS:** Thirty-six rats were randomized to uninjured control, noninvasive ACL rupture (Rupture), and surgical ACL transection (Transection), and 4 and 10 week time points (n = 6 per group). Contrast-enhanced micro-computed tomography (CE-muCT) was employed for AC imaging. Femoral and tibial AC were segmented and converted into thickness maps. Compartmental and sub-compartmental AC thickness and surface roughness (Sa) were computed. OARSI histologic scoring was performed. RESULTS: In both injury groups, zones of adjacent thickening and thinning were evident on the medial femoral condyle, along with general thickening and roughening of femoral and tibial AC. The posterior tibia exhibited diffuse thickening and surface degeneration, and this was worse in Transection. Both injury groups had increased AC thickness and Sa compared to Control at both time points, and Transection exhibited significantly higher Sa in every tibial compartment compared to Rupture. Histologic score was elevated in both groups, and the medial femur exhibited the most severe histologic degeneration. CONCLUSIONS: This is the first 3D quantification of preclinical AC remodeling after ACL injury. Both injury models induced similar changes in AC morphology, but Transection exhibited higher tibial Sa and a greater degree of posterior tibial degeneration. We conclude that AC degeneration is a time-, compartment-, and injury-dependent cascade.


**Full-Text**

**Department of Orthopedic Surgery**

**OBJECTIVE:** Articular cartilage (AC) morphology is an important metric for characterizing degeneration. We propose a novel morphologic analysis using mesh parameterization, enabling the use of surface roughness and thickness metrics to characterize degeneration in a rodent model of post-traumatic osteoarthritis. METHODS: Six rats underwent anterior cruciate ligament transection (ACL-T) and six were controls (Control). At 4-weeks, femora and tibiae were harvested and imaged using contrast-enhanced micro-computed tomography (muCT). Cartilage surfaces were manually outlined, and 2-dimensional thickness maps were generated using mesh
parameterization and analyzed by thickness and surface roughness (Sa). The parameterization technique was validated against the direct distance transform (DDT) and histologic AC thickness from sagittal Safranin-O/Fast-Green sections. Parameterization and DDT measurements were also validated using known, virtual shapes with zero, one, and two planes of curvature. RESULTS: Parameterization had 0.00–6.26% error and DDT had 5.06–12.02% error in determining thicknesses of known shapes. Parameterization thickness correlated highly to DDT thickness (femur: $r = 0.978$, $P < 0.001$; tibia: $r = 0.992$, $P < 0.001$) and histologic thickness (femur: $r = 0.952$, $P < 0.001$; tibia: $r = 0.959$, $P < 0.001$). Thickness maps enabled visualization and quantification of AC degeneration. ACL-T samples displayed general thickening of cartilage, with adjacent regions of thickening and thinning on the medial femoral condyle. Compared to Control, ACL-T thickness was higher in the whole femur, whole tibia, and all compartments and sub-compartments. Sa was higher in the whole femur and medial and lateral condyle, and the whole tibia and medial and lateral plateau. The largest increases in Sa were observed on the medial femoral condyle. CONCLUSIONS: Cartilage analysis using parameterization effectively characterized early degeneration in AC, including sub-compartmental thickening/thinning, and is a powerful tool for assessing degeneration in preclinical osteoarthritis.


Pulsed radiation therapy with concurrent cisplatin results in superior tumor growth delay in a head and neck squamous cell carcinoma murine model.

Purpose: To assess the efficacy of 3-week schedules of low-dose pulsed radiation treatment (PRT) and standard radiation therapy (SRT), with concurrent cisplatin (CDDP) in a head and neck squamous cell carcinoma xenograft model. Methods and Materials: Subcutaneous UT-SCC-14 tumors were established in athymic NIH III HO female mice. A total of 30 Gy was administered as 2 Gy/d, 5 d/wk for 3 weeks, either by PRT (10 x 0.2 Gy/d, with a 3-minute break between each 0.2-Gy dose) or SRT (2 Gy/d, uninterrupted delivery) in combination with concurrent 2 mg/kg CDDP 3 times per week in the final 2 weeks of radiation therapy. Treatment-induced growth delays were defined from twice-weekly tumor volume measurements. Tumor hypoxia was assessed by


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Department of Radiation Oncology

The risk of recurrence following radiation therapy remains high for a significant number of prostate cancer patients. The development of in vitro isogenic models of radioresistance through exposure to fractionated radiation is an increasingly used approach to investigate the mechanisms of radioresistance in cancer cells and help guide improvements in radiotherapy standards. We treated 22Rv1 prostate cancer cells with fractionated 2 Gy radiation to a cumulative total dose of 60 Gy. This process selected for 22Rv1-cells with increased clonogenic survival following subsequent radiation exposure but increased sensitivity toDocetaxel. This RR-22Rv1 cell line was enriched in S-phase cells, less susceptible to DNA damage, radiation-induced apoptosis and acquired enhanced migration potential, when compared to wild type and aged matched control 22Rv1 cells. The selection of radioresistant cancer cells during fractionated radiation therapy may have implications in the development and administration of future targeted therapy in conjunction with radiation therapy.


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Department of Internal Medicine


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Department of Internal Medicine

All available direct oral anticoagulants (DOACs) are at least partially eliminated by the kidneys. These agents are increasingly being used as alternatives to warfarin for stroke prevention in patients with atrial fibrillation. The aim of this study was to identify changes in renal function and associated DOAC dosing implications in a multicenter cohort of atrial fibrillation patients switched from warfarin to DOAC treatment. We included all patients in the Michigan Anticoagulation Quality Improvement Initiative cohort who switched from warfarin to a DOAC with atrial fibrillation as their anticoagulant indication between 2009 and 2014, and who had at least two creatinine values. Compliance with FDA-recommended dosing based on renal function was assessed. Of the 189 patients switched from warfarin to a DOAC, 34 (18.0 %) had a baseline creatinine clearance <50 mL/min and 23 (12.2 %) experienced important fluctuations in renal function. Of these 23 patients, 6 (26.1 %) should have
impacted the DOAC dosing, but only 1 patient actually received an appropriate dose adjustment. Additionally, 15 (7.9%) of patients on DOACs had a dose change performed, but only one patient demonstrated a change in renal function to justify the dose adjustment. Most atrial fibrillation patients who switched from warfarin to a DOAC had stable renal function. However, the majority of patients who had a change in renal function did not receive the indicated dose change. As the use of DOACs expands, monitoring of renal function and appropriate dose adjustments are critical. © 2016, Springer Science+Business Media New York.


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Department of Radiation Oncology


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Department of Diagnostic Radiology and Molecular Imaging

Objectives Illustration of a case of metastatic thyroid cancer with improved uptake and clearance of I-131 from synthetic TSH stimulation versus hormone withdrawal. Methods 68-year old male presenting with hoarseness found to have bilateral thyroid nodules and bilateral cervical lymphadenopathy. The patient was found to have Stage IVa (pT3 pN1b Mx) papillary thyroid cancer status post total thyroidectomy, bilateral neck dissection, and mediastinal lymph node dissection. The patient underwent an I-131 neck and chest scan with dosimetry by serial body and blood sample counting. I-131 scan demonstrated metastatic disease to the mediastinum and lung with thyroid withdrawal and synthetic TSH injections but the clearance of I-131 from the body and blood or marrow was markedly enhanced by synthetic TSG. A subsequent 18F- FDG PET/CT showed additional and concurrent FDG avid lymph nodes and pulmonary nodule. Due to the overwhelming more FDG avid but I-131 non-avid tissue, a second mediastinal dissection was done for metastatic disease to a left paratracheal lymph node that was 18F-FDG and/or I-131 avid. Laboratory work include renal function, LS-MS/MS assay for thyroglobulin (Tg) due to anti-antibodies and a genetic test for BRAF mutation. Results The synthetic TSH stimulated I-131 neck and chest scan and 18F-FDG PET/CT showed significant improvement in positive uptake and the clearance of the I-131 was better in dosimetry study especially in view of mild renal impairment in this BRAF/V600E mutation positive metastatic case. Conclusions The synthetic TSH assisted I-131 SPECT-CT and 18F-FDG PET-CT will enable us to identify the different clones of thyroid metastasis and help the clinical decision for salvage surgical resection before the maximal I-131 was given per dosimetry calculations of bone marrow tolerance. With synthetic TSH injections, these patients can avoid the lengthy discomfort of thyroid hormone withdrawal yet the patient would be maintained at maximal thyroid suppressive therapy. This method would improve I-131 clearance to give the maximal tolerable I-131 dose to treat the metastatic disease.


Request Form
Department of Diagnostic Radiology and Molecular Imaging

Objectives The authors present a case study of suspected necrotizing (malignant) otitis externa, confirmed with Tc99m-MDP bone scan and SPECT-CT. Methods The patient is an 87-year-old male presented with a history of a chronic infection of the right ear with increasing severe otalgia for approximately 5 months despite multiple courses of antibiotics. Medical history is significant for type 2 diabetes, hyperlipidemia, coronary artery disease and known myocardial infarction. CT scan without contrast of the temporal bones was obtained, and the images showed diffuse non-specific irregular wall thickening of the right external auditory canal, without evidence of temporal bone destruction. Mild wall thickening was also noted in the left external auditory canal. Lab tests showed rising ESR. A Tc99m-MDP bone scan was requested to evaluate for clinically suspected necrotizing (malignant) otitis externa. Triple-phase bone scan showed a mild increase in radiotracer accumulation in the blood flow, blood pool and delayed planar images in the right lateral skull when compared to the left. The subsequent SPECT-CT showed moderate increase in radiotracer accumulation in the right external auditory canal, and in the anterior inferior aspect of the right temporal bone, adjacent the temporomandibular joint without involvement of the joint, highly suspicious for osteomyelitis of the right temporal bone, likely secondary malignant otitis externa. Results Further workup such as Gallium scan was declined by the patient. Nevertheless, the findings on the bone scan with hybrid SPECT-CT imaging, in conjunction with positive ear culture of Pseudomonas, is diagnostic for diagnosis of malignant otitis externa in the appropriate clinical setting. The additional finding of osteomyelitis of the right temporal bone made it mandatory for this patient to receive
antibiotics for 6-9 weeks. Conclusions This case illustrates the value of triple-phase bones scan and SPECT-CT imaging in the diagnosis of necrotizing (malignant) otitis externa and providing additional information guiding optimal clinical management of the patients.


Department of Internal Medicine

Background: Definitive concurrent CRT is considered the standard of care for organ preservation and is the only potentially curative therapy in surgically unresectable patients (pts) with stage III-IVb, LA-SCCHN. The standard regimen is 70 Gy (2 Gy/fraction) over 7 weeks with concurrent cisplatin 100 mg/m2 on days 1, 22, and 43. This was established by trials utilizing cisplatin-based CRT. In pts considered to have high risks for adverse events (AEs) with cisplatin, carboplatin has been empirically substituted as an alternative regimen. However, limited data are available regarding the outcomes of pts treated with carboplatin-based CRT. Methods: Data from pts with LA-SCCHN who underwent CRT with carboplatin at our institution in the years 2007-2013 were reviewed. The primary objective was to estimate local-regional control (LRC) rate. Secondary objectives were estimation of progression free survival (PFS), overall survival (OS) as well as laryngectomy rates in LC pts. AEs were assessed according to CTCAE v4. Results: 54 pts with LA-SCCHN who underwent definitive CRT with carboplatin (AUC of 5) were included. Median age was 60.5 (range: 38-80). 42 (78%) were male. 13 (24%) had CKD ≥ stage 3. There were 4 (7%) nonresectable oral cavity (OCC), 19 (35%) oropharyngeal (OPC), 3 (6%) hypopharyngeal (HP), 27 (50%) laryngeal (LC) and 1 (2%) with unknown primary SCCHN. Overall LRC rate was 50% (95% CI 37-63%). The laryngectomy rate in LC pts was 41% (CI 25-59%). Median PFS and OS were 21 (CI 11-33) and 40 (CI 22-61) months, respectively. Stage 11/IVa pts (n = 45) had a median OS of 62 (CI 37-NA) months and 3 year OS of 71% (CI 53-84%) whereas stage IVb (n = 9) had a median OS of 31 (CI 4-NA) months and none survived to 3 years. Dysphagia was the most common AE; 21 pts with grade 2 (39%) and 20 with grade 3 (37%). Myelo-suppression was also common; with grade 3 anemia, neutropenia, and thrombocytopenia seen in 17%, 13% and 15%, respectively. Conclusions: Definitive CRT with carboplatin for LA-SCCHN was well tolerated and demonstrated comparable results to CRT with cisplatin.


A standardized fitness assessment is critical for the development of an individualized exercise prescription. Although the benefits of aquatic exercise have been well established, there remains the need for a standardized non-swimming protocol to accurately assess cardiorespiratory fitness (CRF) in shallow water. The present investigation was designed to assess: 1) reliability of a standardized Shallow Water Run (SWR) test of CRF; and 2) accuracy of a standardized SWR compared with a land-based treadmill test (LTM). Twenty-three healthy females (20 +/- 3 yrs), body mass index (BMI) (23.5 +/- 3 kg/m), performed two shallow water peak oxygen consumption (VO2 peak) running tests (SWR & SWRh) and one VO2max LTM. Intra-class correlation coefficients (ICCs) indicated moderately-strong reliability for VO2peak (ml/kg/min) (r=0.73, p<.01), HRpeak (b/min) (r=0.82, p<.01) and O2pulse (VO2 (ml/kg/min) . (HR(b/min)) (r=0.77, p<.01). Using paired t-tests and Pearson’s correlations, SWR VO2peak and HRpeak were significantly lower than during LTM (p<.05) and showed moderate correlations of 0.60 and 0.58 (p<0.01) to LTM. O2 pulse was similar (p>0.05) for the SWR and LTM tests with a moderate correlation of 0.63. A standardized SWR test as a measure of CRF is a reliable and to some degree, valid alternative to conventional protocols, and may be used by strength and conditioning professionals to measure program outcomes and monitor training progress. Furthermore, this protocol provides a water-based option for CRF assessment among healthy women, and offers insight toward the development of an effective protocol that can accommodate individuals with limited mobility, or those seeking less musculoskeletal impact from traditional land-based types of training. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.


Department of Pathology

Purpose: To investigate associations of bullying and abuse with pelvic floor symptoms, urogenital pain, and sexual health characteristics of women presenting to a multidisciplinary women's urology center. Methods: Retrospective review of a prospective database. Patients completed questions about bullying, abuse, sexual health and validated questionnaires including the Pelvic Floor Distress Inventory (PFDI-20), Overactive Bladder Questionnaire (OAB-q), and visual analog scale (VAS 0–10) for genitourinary pain. Statistical analyses included Chi-squared and t-tests, which compared victims of bullying and/or abuse to non-victims. Results: Three hundred and eighty patients were reviewed. Three hundred and thirty-eight had data on bullying and abuse history. Out of 380, 94 (24.7%) reported that they were victims of bullying. Out of 380, 104 (27.4%) reported that they were victims of abuse. Women with a history of bullying and abuse had increased overall pain scores compared to those without a history of either. Women with a history of abuse and bullying had increased PFDI-20, POPDI, and UDI-6 scores compared to women who were not bullied or abused. There was no difference in being sexually active or in sexual satisfaction between the groups. Patients with a history of abuse and bullying had the greatest percentage of dyspareunia (p = 0.009). Conclusions: Women with a history of bullying, abuse, or both predict increased pelvic floor distress, urological symptoms, increased urogenital pain, and increased dyspareunia. Clinicians should screen for exposure to bullying or abuse in order to provide comprehensive resources to address these psychosocial issues. © 2016 Springer Science+Business Media Dordrecht.


Department of Pediatrics

Objective: To determine independent perinatal and intrapartum factors associated with neonatal hypoglycemia. Method: Of singleton pregnancies delivered at term in 2013; 318 (3.8%) neonates diagnosed with hypoglycemia were compared to 7955 (96.2%) neonate controls with regression analysis. Results: Regression analysis showed that independent prenatal factors were multiparity (odds-ratio [OR] = 1.61), gestational age (OR = 0.68), gestational diabetes (OR = 0.22), macrosomia (OR = 4.87), small for gestational age neonate [SGA] (OR = 6.83) and admission cervical dilation (OR = 0.79). For intrapartum factors, only cesarean section (OR = 1.57) and last cervical dilation (OR = 0.92) were independently significantly associated with neonatal hypoglycemia. For biologically plausible risk factors, independent factors were cesarean section (OR = 4.18), gentamycin/clindamycin in labor (OR = 5.35), gestational age (OR = 0.59) and macrosomia (OR = 5.62). Mothers of babies with neonatal hypoglycemia had more blood loss and longer hospital stays, while neonates with hypoglycemia had worse umbilical cord gases, more neonatal hypoxic conditions, neonatal morbidities and
Purpose: Fibrotic changes after stereotactic body radiation therapy (SBRT) for stage I non-small cell lung cancer (NSCLC) are difficult to distinguish from local recurrences (LR), hampering proper patient selection for salvage therapy. This study validates previously reported high-risk computed tomography (CT) features (HRFs) for detection of LR in an independent patient cohort. Methods and Materials: From a multicenter database, 13 patients with biopsy-proven LR were matched 1:2 to 26 non-LR control patients based on dose, planning target volume (PTV), follow-up time, and lung lobe. Tested HRFs were enlarging opacity, sequential enlarging opacity, enlarging opacity after 12 months, bulging margin, linear margin disappearance, loss of air bronchogram, and craniocaudal growth. Additionally, 2 new features were analyzed: the occurrence of new unilateral pleural effusion, and growth based on relative volume, assessed by manual delineation. Results: All HRFs were significantly associated with LR except for loss of air bronchogram. The best performing HRFs were bulging margin, linear margin disappearance, and craniocaudal growth. Receiver operating characteristic analysis of the number of HRFs to detect LR had an area under the curve (AUC) of 0.97 (95% confidence interval [CI] 0.9-1.0), which was identical to the performance described in the original report. The best compromise (closest to 100% sensitivity and specificity) was found at >= 4 HRFs, with a sensitivity of 92% and a specificity of 85%. A model consisting of only 2 HRFs, bulging margin and craniocaudal growth, resulted in a sensitivity of 85% and a specificity of 100%, with an AUC of 0.96 (95% CI 0.9-1.0) (HRFs >= 2). Pleural effusion and relative growth did not significantly improve the model. Conclusion: We successfully validated CT-based HRFs for detection of LR after SBRT for early-stage NSCLC. As an alternative to number of HRFs, we propose a simplified model with the combination of the 2 best HRFs: bulging margin and craniocaudal growth, although validation is warranted. (C) 2016 Elsevier Inc. All rights reserved.
groups were comparable. Mean duration of postoperative follow-up was 41.4 weeks (±49.0). Of 59 eyes, 33 (55.9%) exhibited an ERM intraoperatively. Four ERM (SD-OCT group) compared to 12 (TD-OCT group) were not visualized on preoperative OCT (p = 0.003). Sensitivity and specificity of SD-OCT in ERM detection was 79% and 100% compared to 14% and 91% for TD-OCT. Visual acuity improved in both arms (0.5 and 0.3 logMAR units in SD-OCT and TD-OCT, respectively (p = 0.002, 0.0002). CONCLUSIONS: We found that SD-OCT was superior to TD-OCT in identifying the presence of ERM preoperatively in patients who underwent macular hole surgery. Since ERM may decrease the chance of successful pharmacologic vitreolysis, we recommend using SD-OCT over TD-OCT in the evaluation of patients with FTMH to more accurately identify ERMs and allow more comprehensive treatment decisions (pharmacologic versus surgical).


Department of Ophthalmology

Purpose: To compare the incidence and clinical features of endophthalmitis after intravitreal antiangiogenic endothelial growth factor (VEGF) therapy for diabetic eye disease, neovascular age-related macular degeneration (AMD) and retinal vein occlusion (RVO). Methods: Multicentre, retrospective, consecutive case-control study. All patients treated with intravitreal bevacizumab, ranibizumab or aflibercept for diabetic eye disease, neovascular AMD or RVO between 1 January 2009 and 30 September 2013 at three retina practices were included in this study. The total number of antiVEGF injections administered for the three indications was calculated using billing records. Endophthalmitis cases were identified using both endophthalmitis log sheets and billing records. Patient charts were reviewed to confirm that endophthalmitis was directly related to anti-VEGF injection and to record clinical features and culture results. Results: During the study period, a total of 353 978 intravitreal anti-VEGF injections were performed. Presumed infectious endophthalmitis occurred in 119 of 296 017 injections performed for neovascular AMD (1/2487, 0.04%), 12 of 24 541 for diabetic eye disease (1/2045, 0.049%) and 4 of 32 418 for RVO (1/8104, 0.012%). X2 analysis found endophthalmitis rates to be higher in diabetic eye disease compared with RVO (p=0.010) and higher in neovascular AMD compared with RVO (p=0.014), while diabetic eye disease and neovascular AMD (p=0.517) had similar rates. The average age of the overall neovascular AMD patient population (81.9 years) was significantly older than the diabetic eye disease (64.7 years, p<0.001) and RVO (73.4 years, p<0.001) populations. Conclusions: Endophthalmitis rates appear to be lower in eyes with RVO compared with diabetic eye disease and neovascular AMD, possibly due to impaired immunity in diabetics and waning immunity in the generally older AMD population.


Full-Text

OUWB Medical Student Author

Department of Ophthalmology

Purpose: The aim of the study was to present the long-term anatomical and visual outcomes of retinal detachment repair in patients with Stickler syndrome. Patients and methods: This study is a retrospective, interventional, consecutive case series of patients with Stickler syndrome undergoing retinal reattachment surgery from 2009 to 2014 at the Associated Retinal Consultants, William Beaumont Hospital. Results: Sixteen eyes from 13 patients were identified. Patients underwent a mean of 3.1 surgical interventions (range: 1–13) with a mean postoperative follow-up of 94 months (range: 5–313 months). Twelve eyes (75%) developed proliferative vitreoretinopathy. Retinal reattachment was achieved in 100% of eyes, with ten eyes (63%) requiring silicone oil tamponade at final follow-up. Mean preoperative visual acuity (VA) was 20/914, which improved to 20/796 at final follow-up (P=0.81). There was a significant correlation between presenting and final VA (P<0.001), and patients with poorer presenting VA were more likely to require silicone oil tamponade at final follow-up (P=0.04). Conclusion: Repair of retinal detachment in patients with Stickler syndrome often requires multiple surgeries, and visual outcomes are variable. Presenting VA is significantly predictive of long-term VA outcomes. © 2016 Reddy et al.


Full-Text

Department of Internal Medicine

Background: Microvascular inflammation (MVI), assessed as glomerulitis (g) + peritubular capillaritis (ptc), is associated with T cell mediated (CMR) and antibody mediated (AMR) allograft rejection. It is a key finding in diagnosis of C4d-negative AMR. For that reason it was incorporated into the 2013 update of the Banff classification. There is high observer variability however. We observed a high proportion of MVI cells in
allograft rejection are activated cytotoxic T cells with aggregated perforin-positive granules detectable by immunohistochemistry (IHC). Perforin positive cells are rare in the interstitium and tubules. In this setting the perforin stain is a stain for MVI. We sought to determine whether it could substitute for the calculation of MVI.

Design: Fifty clinically indicated renal allograft biopsies were selected to include various classes of rejection based on the 2013 Banff criteria. Perforin IHC was performed on each biopsy using a mouse monoclonal antibody, and the number of perforin positive cells per 10 high power fields (400X) was counted blindly and recorded. Results: Table 1. Mean perforin positive cells per 10 high power fields (hpf) in renal transplant biopsies grouped by Banff classification. Cases of CMR graded at 1B or higher, and cases of AMR had increased perforin counts per unit area over cases with no acute rejection or CMR 1a (p<0.05). Cases of AMR had higher mean perforin counts than patients with either 1B or 2 ACR (p<0.05). Conclusion: Perforin counts show the same associations with allograft rejection as previously shown for MVI. The perforin count stratifies patients into three risk groups: 1. no rejection and CMR 1a, 2. CMR 1b and 2, and 3. AMR. Perforin-positive lymphocytes in peritubular capillaries in an allograft biopsy (400X). (Figure Presented).


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Department of Obstetrics and Gynecology

An abstract of the article "A novel customisable sensitivity and specificity driven standardisation of early fetal echocardiography by TVS (transvaginal sonography)" by S. Rottem and colleagues is presented.


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Department of Obstetrics and Gynecology

An abstract of the article "Markers and intelligent agent driven early fetal echocardiography in lieu of the conventional views-focused scanning method," by S. Rottem and colleagues is presented.


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Department of Obstetrics and Gynecology

An abstract of the article "Contribution of morphologic and biometric markers to detection of 22 congenital heart defects (CHDs) by transvaginal sonography at 9-14 weeks of gestation," by S. Rottem and colleagues is presented.


Full-Text

Department of Internal Medicine


Full-Text

Department of Internal Medicine


Full-Text

Department of Internal Medicine

Professional societies recommend embolic protection devices (EPDs) during percutaneous intervention of saphenous vein bypass grafts (SVGs; class I, level of evidence B). Practice patterns indicate that 21% of SVG interventions are performed with EPDs. Despite a single randomized trial that demonstrated efficacy for EPDs, other studies suggest that the benefits of EPDs are controversial. Consideration should be given toward performing a contemporary EPD trial to incorporate new technologies and pharmacotherapies; in the meantime, guideline recommendations for use of EPDs should be downgraded.
Background: High grade gliomas carry a grim prognosis despite current therapies. Several studies have shown that the combination of anti-PD-1 antibody with stereotactic radiosurgery generates robust and durable responses and improves survival in preclinical models of glioma. Pembrol is a highly selective humanized monoclonal antibody against PD-1. This study evaluates the safety and anti-tumor activity of Pembrol administered in combination with Bev and HFSRT in pts with recurrent high grade gliomas. Methods: This phase I study (3+3 design) explores the safety, tolerability, recommended phase II dose (RP2D), and antitumor activity of Pembrol administered concurrently with HFSRT and Bev (NCT02313272 ). Adult pts with recurrent glioblastoma (GBM) or anaplastic astrocytoma (maximum diameter of target lesion ≤ 3.5 cm) are eligible. Eligible patients receive HFSRT to the recurrent tumor (30 Gy delivered in 5 fractions) combined with Bev (10 mg/kg, intravenously Q2W) and Pembrol (100 mg or 200 mg intravenously based on dose level, Q3W). Two dose levels of Pembrol (100 mg and 200 mg Q3W) are explored. Once the RP2D is determined, an additional 20 patients will be enrolled in an expansion cohort. Response is assessed every 6W per RANO criteria. Effect of treatment on quality of life measures are evaluated. Results: As of Feb 2016, 6 pts with GBM were enrolled: 3 at Pembrol 100 mg, 3 at Pembrol 200 mg dose levels. No dose limiting toxicity or dose modifications were reported. Permanent discontinuation due to treatment-related AEs has not occurred. No treatment related neurologic AEs were observed. The most common drug-related AE was grade 1 fatigue (2 out of 6). At the time of abstract submission, all pts are continuing on study treatment and 3 pts (at Pembrol 100 mg dose level) are evaluable for response. Durable disease control is seen in all 3 pts, including 1 CR (24+W) and 2 SDs (24+ W and 22 + W). Conclusions: Preliminary data demonstrate an acceptable toxicity profile for combination of HFSRT with Pembrol and Bev in pts with recurrent high grade gliomas. Updated safety, efficacy data will be presented.
Charitable meal services are crucial in sustaining the homeless, but few use nutritional professionals to create a balanced diet or make adjustments for those with specific dietary needs. A needs assessment was conducted among church coordinators responsible for providing meals to clients at a multi-service shelter in Detroit, Michigan. A survey and focus group were used to assess the processes involved in planning, preparing, and providing meals, which provided critical information and insight concerning nutrition and factors influencing meal-planning. According to the survey, a majority of faith organizations responding tried to meet food group requirements every meal. A predominant theme from the focus group was the desire to satisfy clients resulting in a variety and abundance of food enabling poor choices. The provision of healthy options was constrained by efforts to ease meal preparation, desire to provide comfort foods, and having difficulties accommodating diets related to health problems. © Meharry Medical College.

leiomyomatosis renal cell carcinoma syndrome (HLRCC), show fumarate hydratase (FH) gene mutation and loss of function. On the basis of similar cytomorphology and clinicopathologic features between these tumors and cases described as tubulocystic carcinomas with poorly differentiated foci (TC-PD) of infiltrative adenocarcinoma, we hypothesized a relationship between these entities. First, 29 RCCs with morphology of TC-PD were identified retrospectively and assessed for FH expression and aberrant succionation (ZSC) by immunohistochemistry (IHC), with targeted next-generation sequencing of 409 genes-including FH-performed on a subset. The 29 TC-PD RCCs included 21 males and 8 females, aged 15 to 76 years (median, 46), with tumors measuring 2 to 21 cm (median, 9) arising in the right (n=16) and left (n=13) kidneys. Family history or stigmata of HLRCC were identifiable only retrospectively in 3 (12%). These tumors were aggressive, with 79% showing perinephric extension, nodal involvement in 41%, and metastasis in 86%. Of these, 16 (55%) demonstrated loss of FH by IHC (14/14 with positive ZSC). In contrast, 5 (17%) showed a wild-type immunoprofile of FH+/ZSC-. An intriguing group of 8 (28%) showed variable FH+/- positivity, but with strong/diffuse ZSC+. Next-generation sequencing revealed 8 cases with FH mutations, including 5 FH−/ZSC+ and 3 FH+/ZSC+ cases, but none in FH+/ZSC− cases. Secondly, we retrospectively reviewed the morphology of 2 well-characterized cohorts of RCCs with FH-deficiency determined by IHC or sequencing (n=23 and n=9), unslected for TC-PD pattern, identifying the TC-PD morphology in 10 (31%). We conclude that RCCs with TC-PD morphology are enriched for FH deficiency, and we recommend additional workup, including referral to genetic counseling, for prospective cases. In addition, based on these and other observations, we propose the term "FH-deficient RCC" as a provisional term for tumors with a combination of suggestive morphology and immunophenotype but where genetic confirmation is unavailable upon diagnosis. This term will serve as a provisional nomenclature that will enable triage of individual cases for genetic counseling and testing while designating these cases for prospective studies of their relationship to HLRCC.


**Department of Surgery**

Objective: To determine the pediatric incidence and association of superior semicircular canal dehiscence (SSCD) with inner ear (IE) anomalies. Study Design: Retrospective chart review. Setting: Two tertiary referral centers. Patients: Children less than 18 years who received a 0.5mm or less collimated computed tomography study including the temporal bones between 2010 and 2013 for reasons including, but not limited to, hearing loss, trauma, and infection. Interventions: Images were reformatted into Pöschl and Stenver planes. Five hundred three computed tomography studies (1,006 temporal bones) were reviewed by experienced, blinded neuroradiologists. Main Outcome Measures: Incidence of SSCD and IE anomalies. Patient age, sex, and diagnosis were recorded. Statistical analysis was performed to compare outcome measures among patient demographics. Results: The incidence of SSCD was 6.2% (31/503) and an IE anomaly was 15.1% (76/503) of individuals. The incidence of SSCD with an IE anomaly was not significantly correlated (1.1%, 40/1,006; p=0.23; LR=+1.29). The mean age of children with SSCD was lower (5.9 versus 9.8 yr; p=0.002). SSCD incidence decreased with age (ages <2, 2-8, and 9-18 yr were 36.7%, 5.6%, and 3.2%; p=0.001) and SSC bone thickness nonsignificantly increased with age. Children with SSCD were commonly male (74.2%, p=0.041). Conclusion: SSCD and IE anomalies are unlikely related. SSCD incidence is highest in children <2 years, with SSC bone increasing until 2 to 8 years of age. This supports the theory of a congenital precedent to SSCD, with overlying bone maturation occurring during early childhood. Age <2 years was a significant predictor of SSCD.


**Department of Pathology**

Inadequate dietary Zn consumption increases susceptibility to esophageal and other cancers in humans and model organisms. Since Zn supplementation can prevent cancers in rodent squamous cell carcinoma (SCC) models, we were interested in determining if it could have a preventive effect in a rodent skin cancer model, as a preclinical basis for considering a role for Zn in prevention of human nonmelanoma skin cancers, the most frequent cancers in humans. We used the 7,12-dimethyl benzanthracene carcinogen/phorbol myristate acetate tumor promoter treatment method to induce skin tumors in Zn-sufficient wild-type and Fhit (human or mouse protein) knockout mice. Fhit protein expression is lost in >50% of human cancers, including skin SCCs, and Fhit-deficient mice show increased sensitivity to carcinogen induction of tumors. We hypothesized that: (1) the skin cancer burdens would be reduced by Zn supplementation; (2) Fhit(-/-) Fhit, murine fragile histidine triad gene) mice would show increased susceptibility to skin tumor induction versus wild-type mice. 30 weeks after initiating treatment, the tumor burden was increased similar to 2-fold in Fhit(-/-) versus wild-type mice (16.2 versus 7.6 tumors, P<0.001); Zn supplementation significantly reduced tumor burdens in Fhit(-/-) mice (males
and females combined, 16.2 unsupplemented versus 10.3 supplemented, P=0.001). Most importantly, the SCC burden was reduced after Zn supplementation in both strains and genders of mice, most significantly in the wild-type males (P=0.035). Although the mechanism(s) of action of Zn supplementation in skin tumor prevention is not known in detail, the Zn-supplemented tumors showed evidence of reduced DNA damage and some cohorts showed reduced inflammation scores. The results suggest that mild Zn supplementation should be tested for prevention of skin cancer in high-risk human cohorts.


Department of Radiation Oncology


Department of Pathology
Paraneoplastic dermatoses are skin disorders that are associated with malignancy. Anaplastic large T-cell lymphoma (ALTCL) has rarely been associated with paraneoplastic skin manifestations such as gangrenous foot ulcers and erythroderma. Methods: We describe a case of ALTCL presenting as a large annular skin rash. The clinical picture, course, and treatment will be discussed along with current hypotheses on the mechanism of paraneoplastic syndromes. Results: Skin manifestations in ALTCL most commonly arise in two distinct ways; either as primary cutaneous lymphoma manifestation or as systemic disease with secondary metastasis. Less commonly, systemic disease causes skin manifestations secondary to a paraneoplastic process without infiltration of malignant cells. This is thought to be mediated by an immunologic reaction to tumor antigen or the result of cytokines and other inflammatory markers produced by the tumor itself. Conclusion: Paraneoplastic dermatoses could be the initial presentations of systemic lymphoma. Knowledge about their association with anaplastic large-cell lymphoma may help with timely diagnosis. In a patient with unexplained dermatosis associated with B symptoms who is unresponsive to topic treatment, an investigation for systemic lymphoma workup is warranted.


Department of Ophthalmology


OUWB Medical Student Author

PURPOSE:: To report the visual acuity outcomes after pars plana vitrectomy for delayed vitreoretinal sequelae of infectious endophthalmitis. All eyes were initially treated with intravitreal antibiotics (Abx). METHODS:: Multicenter, retrospective, consecutive case series. RESULTS:: Forty-two eyes met the study criteria. The mean follow-up was 48 weeks (SD ± 61.8). Mean interval from Abx to pars plana vitrectomy was 13 weeks (SD ± 14.3, range 2–70). Indications for pars plana vitrectomy included vitreous opacities (VO) (n = 22), epiretinal membrane (n = 9), and retinal detachment (n = 11). LogMAR visual acuity improved from 1.87 (Snellen equivalent: 20/1,482) preoperatively to 1.35 (Snellen equivalent: 20/447) at final evaluation (P < 0.001). LogMAR visual acuity improved significantly for patients with vitreous opacities (P < 0.01) and retinal detachment (P = 0.02) but not for patients with epiretinal membranes (P = 0.08). CONCLUSION:: Patients with infectious endophthalmitis can gain vision if they have a pars plana vitrectomy for delayed sequelae such as vitreous opacities or for retinal detachment. © 2016 by Ophthalmic Communications Society, Inc.


Department of Ophthalmology
Objective: To compare the effects of intravitreal ranibizumab (RZB) or dexamethasone (DEX) intravitreal implant in cases of recalcitrant diabetic macular edema (DME). Methods: Retrospective, interventional study examining patients with symmetric bilateral, center-involved DME recalcitrant to treatment with RZB, who received DEX in one eye while the contralateral eye continued to receive RZB every 4–5 weeks for a study period of 3 months. Results: Eleven patients (22 eyes) were included: mean logarithm of the minimal angle of resolution (logMAR) visual acuity (VA) for the DEX arm improved from 0.415 (standard deviation [SD] ±0.16) to 0.261 (SD ±0.18) at final evaluation, and mean central macular thickness (CMT) improved from 461 µm (SD ±156) to 356 µm (SD ±110; net decrease: 105 µm, P=0.01). Mean logMAR VA for the RZB arm improved from 0.394 (SD ±0.31) to 0.269 (SD ±0.19) at final evaluation. Mean CMT improved from 421 µm (SD ±147) to 373 µm (SD ±129; net decrease: 48 µm, P=0.06). Conclusion: A subset of recalcitrant DME patients demonstrated significant CMT reduction and VA improvement after a single DEX injection. © 2016 Thomas et al.

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Department of Biomedical Sciences (OU)

In the Gross Anatomy laboratory, students are introduced to the first person that has entrusted them with the care of their body. The laboratory is also an excellent place to learn to appreciate anatomical diversity and the impact that pathological processes have on the body. At Oakland University William Beaumont School of Medicine (OUWB) we are striving to increase the ways students interact with donated cadavers and increase the communication of anatomical and pathological findings with their classmates. To further this effort, we implemented a cadaver assessment form for students to document physical findings, anatomical variations and pathological findings. Utilizing the student observations from these forms, we are building a laboratory photographic eBook record. For example, students have documented anatomical variations such as a third head of the biceps brachii, variations in the arterial branches of the aortic arch, hepatomegaly, splenomegaly and enlarged hearts. They have also found evidence of multiple surgical procedures and cancerous pathologies. At the end of the course, a team of pathologists will participate in a special session to discuss the pathologies found during the semester and their clinical correlates. Students will be surveyed at the end of the semester to evaluate how this project has impacted student communication of anatomical and pathological findings with their classmates.

Department of Ophthalmology

In this report, the authors describe the technique of using a 27-gauge vitrectomy platform to perform pars plana vitrectomy, lensectomy, and sutureless scleral IOL fixation in a patient with crystalline lens dislocation secondary to Marfan’s syndrome. Case report and detailed description of the surgical technique are discussed. © 2016, Slack Incorporated. All rights reserved.

Department of Obstetrics and Gynecology

OBJECTIVE: To evaluate whether therapy with sildenafil citrate prolongs gestation in women with preeclampsia. METHODS: In a randomized double-blind, placebo-controlled trial, 100 singleton pregnancies with preeclampsia between 24 and 33 weeks of gestation were randomized to 50 mg oral sildenafil citrate every 8 hours or placebo. The primary outcome was prolongation of pregnancy from randomization to delivery. Secondary outcomes were changes in resistance indices of uterine, umbilical, and middle cerebral arteries by Doppler, fetal and maternal complications, and adverse neonatal outcomes. Power analysis estimated that to detect a difference of 5 days in pregnancy duration, 43 patients would have to be randomized to each group. RESULTS: From June 2013 to October 2015, 50 patients were randomized to each group. Pregnancy duration was on average 4 days longer (14.4 days, 95% confidence interval [CI] 12.5-16.6 days compared with 10.4 days, 95% CI 8.4-12.3 days, P=.008) and percent reduction in pulsatility indices of uterine and umbilical arteries higher (22.5% and 18.5%, compared with placebo 2.1% and 2.5%, P <.001) for patients treated with sildenafil compared with placebo. Maternal blood pressure before and 24 hours after randomization was lower with sildenafil (sildenafil: 100.3 +/- 5.6 mm Hg compared with 116.4 +/- 5.1 mm Hg, P <.05; placebo: 110.6 +/- 6.2 mm Hg compared with 114.7 +/- 6.5 mm Hg, P=.21). There was no difference in perinatal morbidity, mortality,

Full-Text

Department of Radiation Oncology

Purpose: To pool data across multiple institutions internationally and report on the cumulative experience of brainstem stereotactic radiosurgery (SRS). Methods and Materials: Data on patients with brainstem metastases treated with SRS were collected through the International Gamma Knife Research Foundation. Clinical, radiographic, and dosimetric characteristics were compared for factors prognostic for local control (LC) and overall survival (OS) using univariate and multivariate analyses. Results: Of 547 patients with 569 brainstem metastases treated with SRS, treatment of 7.4% of tumors resulted in severe SRS-induced toxicity (grade ≥3, increased odds with increasing tumor volume, margin dose, and whole-brain irradiation). Local control at 12 months after SRS was 81.8% and was improved with increasing margin dose and maximum dose. Overall survival at 12 months after SRS was 32.7% and impacted by age, gender, number of metastases, tumor histology, and performance score. Conclusions: Our study provides additional evidence that SRS has become an option for patients with brainstem metastases, with an excellent benefit-to-risk ratio in the hands of experienced clinicians. Prior whole-brain irradiation increases the risk of severe toxicity in brainstem metastasis patients undergoing SRS. © 2016 Elsevier Inc.


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OUWB Medical Student Author


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Department of Urology

Overlapping symptoms of overactive bladder (OAB) and urinary tract infection (UTI) often complicate the diagnosis and contribute to overprescription of antibiotics. Inflammatory response is a shared characteristic of both UTI and OAB and here we hypothesized that molecular differences in inflammatory response seen in urine can help discriminate OAB from UTI. Subjects in the age range of (20 – 88 yr) of either sex were recruited for this urine analysis study. Urine specimens were available from 62 UTI patients with positive dipstick test before antibiotic treatment. Six of these patients also provided urine after completion of antibiotic treatment. Subjects in cohorts of OAB (n = 59) and asymptomatic controls (n = 26) were negative for dipstick test. Urinary chemokines were measured by MILLIPLEX MAP Human Cytokine/ Chemokine Immunoassay and their association with UTI and OAB was determined by univariate and multivariate statistics. Significant elevation of CXCL-1, CXCL-8 (IL-8), and CXCL-10 together with reduced levels for a receptor antagonist of IL-1α (sIL-1RA) were seen in UTI relative to OAB and asymptomatic controls. Elevated CXCL-1 urine levels predicted UTI with odds ratio of 1.018 and showed a specificity of 80.77% and sensitivity of 59.68%. Postantibiotic treatment, reduction was seen in all CXC chemokines with a significant reduction for CXCL-10. Strong association of CXCL-1 and CXCL-10 for UTI over OAB indicates mechanistic differences in signaling pathways driving inflammation secondary of infection in UTI compared with a lack of infection in OAB. Urinary chemokines highlight molecular differences in the paracrine signaling driving the overlapping symptoms of UTI and OAB. © 2016 the American Physiological Society.


Full-Text

OUWB Medical Student Author

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Department of Orthopedic Surgery

Video recordings of surgical procedures are an excellent tool for presentations, analyzing self-performance, illustrating publications, and educating surgeons and patients. Recording the surgeon's perspective with high-resolution video in the operating room or clinic has become readily available and advances in software improve the ease of editing these videos. A GoPro HERO 4 Silver or Black was mounted on a head strap and worn over the surgical scrub cap, above the loupes of the operating surgeon. Five live surgical cases were recorded with the camera. The videos were uploaded to a computer and subsequently edited with iMovie or the GoPro software. The optimal settings for both the Silver and Black editions, when operating room lights are used, were determined to be a narrow view, 1080p, 60 frames per second (fps), spot meter on, protune on with auto white balance, exposure compensation at -0.5, and without a polarizing lens. When the operating room lights were not used, it was determined that the standard settings for a GoPro camera were ideal for positioning and editing (4K, 15 frames per second, spot meter and protune off). The GoPro HERO 4 provides high-quality, the surgeon perspective, and a cost-effective video recording of upper extremity surgical procedures. Challenges include finding the optimal settings for each surgical procedure and the length of recording due to battery life limitations.

Full-Text

Department of Anesthesiology

Study objective The prevalence of anesthesiology department wellness programs is unknown. A database of wellness programs is needed as a resource for departments attempting to respond to the Accreditation Council for Graduate Medical Education Anesthesiology Milestones Project. The purpose of this study was to survey academic anesthesiology chairs on wellness issues, characterize initiatives, and establish wellness contacts for a Wellness Initiative Database (WID). Design An Internet-based survey instrument was distributed to academic anesthesiology department chairs in the United States. Setting On-line. Patients None. Interventions None. Measurements Analysis for continuous variables used standard means, modes, and averages for individual responses; 95% confidence intervals for proportions were calculated by Wilson's method. Main results Seventy-five (56.4%) responses (of a potential 133 programs) were obtained. Forty-one (of 71 responders; 57.8%) expressed interest in participating in a WID, and 33 (44%) provided contact information. Most (74.7%) had recently referred staff for counseling or wellness resources, yet many (79.5% and 67.1%, respectively) had never surveyed their department’s interest in wellness resources. Thirty-four percent had a wellness resources repository. Of 22 wellness topics, 8 garnered >60% strong interest from respondents: Addiction Counseling, Sleep Hygiene, Peer Support Program, Stress Management, Conflict Management, Burnout Counseling, Time Management, and Dealing with Adverse Events Training. There was a statistically significant difference in interest between those willing to participate or not in the WID across most topics but no significant difference based on need for recent staff referral. Conclusions The majority of chairs needed to recently refer a department member to wellness resources or counseling. Most were interested in participating in a WID, whereas a minority had gauged staff interest in wellness topics or had a wellness resource repository. Highest interest was in topics most related to function as an anesthesiologist. Those willing to participate in the database had statistically significant differences in interest across most wellness topics. © 2016 Elsevier Inc.


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Department of Emergency Medicine

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Department of Radiation Oncology

Purpose: To compare clinical outcomes (CO) in patients with high risk (HR), very high risk (VHR), and favorable high risk (FHR) prostate cancer receiving definitive dose escalated radiotherapy using image-guided adaptive radiotherapy (IGART) vs. high-dose rate brachytherapy boost (HDR-B). Materials/Methods: The sample consisted of patients with HR prostate cancer treated with definitive radiotherapy between Feb. 1992-Oct. 2013 using IGART or HDR-B. Using NCCN Guidelines, 571 patients were categorized with HR prostate cancer: T3a, Gleason B-10, or PSA 20 ng/ml. A matched pair analysis was completed to compare CO between treatment modalities using the following criteria: PSA group (<4, 4-10, 10-20, ≥20), Gleason (≤7, 8, 9-10), T-stage (≤T2a, >T2b), age ≤3 yrs., and androgen suppression (yes, no). Patients with < 6 months or with a pre-tx PSA > 50 were excluded. Two subset analyses were completed to examine CO in VHR (T3b-T4, primary Gleason pattern 5, and/or >4 cores with Gleason 8-10), and FHR prostate cancer (T1c, Gleason 8, and PSA <20). Patients were compared using two-tailed t tests (continuous) and Pearson’s c2 test (categorical).

Outcomes were calculated using Kaplan–Meier’s Log-rank test. Univariate analyses (UVA) and multivariate (MVA) were computed using the Cox Regression model to determine if differences in CO were affected by patient characteristics, treatment type, and the Charlson Comorbidity Index (CCI). Results: The matched pair analysis yielded 130 pairs of patients who met the inclusion criteria, which constituted the final cohort of patients (n=260). Follow-up time was significantly higher for the HDR-B group (p<0.001), with a median duration of 7.6 yrs. vs. 5.8 yrs. for IGART. Higher rates of biochemical control (BC) (p=0.028) were observed in the HDR-B group vs. IGART (Table 1). There were no differences between the groups for survival or local recurrence. While not significant, the rates of distant metastasis were lower in the HDR-B group (Table 1). Our subset analysis showed the VHR cohort (n=84) to have significantly inferior rates of BC, distant metastasis (DM), cause-specific survival (CSS), and disease free survival (DFS). When evaluating the FHR cohort (n=45) increased BC was seen, 89.5% vs. 71.6% at 5 yrs. & 89.5% vs. 60.6% at 10 yrs. when compared to the remaining patients (p<0.017). No differences were (Table Presented) seen in CO within FHR & VHR subgroups when compared by treatment type. UVA for the entire group of patients treated with IGART (n=130) revealed the following correlations to BC: pre-tx PSA continuous (p<0.02), pre-tx PSA categorical (p<0.048), & nadir (p<0.001), none of which were no longer significant on MVA. HDR-B exhibited significant findings only for nadir (p<0.001), CCI did not impact BC rates. Conclusions: Excellent clinical outcomes were observed for HR prostate cancer patients regardless of treatment type; however, HDR-B resulted in superior benefit in BC rates. Despite significant differences in CO for VHR & FHR patients, respectively, treatment type was not associated with differences in clinical or biochemical endpoints for these subgroups.


Department of Pathology
Department of Internal Medicine
Department of Radiation Oncology

BACKGROUND: The purpose of the study was to determine outcomes for patients treated with accelerated partial breast irradiation (APBI) on the basis of breast cancer subtype (BCST). PATIENTS AND METHODS: Our single-institution, institutional review board-approved APBI database was queried for patients who had complete testing results for the estrogen (ER), progesterone (PR), and HER2/neu receptors to determine outcomes for each BCST. Women were assigned as luminal A (LA), luminal B (LB), HER2, and basal BCST using their ER, PR, and HER2/neu receptor status. Degree of ER expression supplemented the receptor-based luminal BCST assignment. Two hundred seventy-eight patients had results for all 3 receptors (LA = 164 [59%], LB = 81 [29%], HER2 = 5 [2%], basal = 28 [10%]), which were submitted for analysis [ipsilateral breast tumor recurrence [IBTR], regional nodal failure, distant metastasis [DM], disease-free survival [DFS], cause-specific survival [CSS], and overall survival [OS]]. RESULTS: Median follow-up was 5.4 years (range, 0.1-12.4 years). Basal and HER2 subtype patients had higher histologic grades (Grade 3 = 75% vs. 10% LA/LB; P < .001), larger tumors (13.0 mm basal vs. 10.7 mm LA/LB; P = .059), and were more likely to receive chemotherapy (68% vs. 15% LA/LB; P < .001). Margin and nodal status were similar among BCSTS. At 5 years, IBTR rates were similar (18%, 2%, 0%, and 4.8%) for LA, LB, HER2, and basal subtypes, respectively (P = .62). DM was only seen in LA (2.9%) and LB (1.3%) (P = .83). DFS (95%-100%), CSS (97%-100%), and OS (80%-100%) were not statistically different (P = .97, .87, .46, respectively). CONCLUSION: Five-year local control rates after breast-conserving surgery, APBI, and appropriate systemic therapy are excellent for luminal, HER2, and basal phenotypes of early-stage breast cancer; however, further study of receptor subtype effect on risk stratification in early-stage breast cancer is needed.

INTRODUCTION: Although whole breast irradiation (WBI) represents the standard radiotherapy technique in breast conserving therapy, accelerated partial breast irradiation (APBI) has emerged as an option to reduce treatment duration with comparable clinical outcomes. The purpose of this analysis is to present long-term clinical outcomes between WBI and APBI. METHODS: A total of 3009 patients were treated with breast conserving therapy at a single institution between 1980 and 2012. Among them, 2528 patients received WBI and 481 received APBI (interstitial or balloon based). A matched-pair analysis was performed with patients matched by age (+/-3 years), stage (T-stage vs. T1 vs. T2), and estrogen receptor status (+/-). All patients had a minimum of 12 months follow-up. A total of 274 matches (ratio 1:1) were made. RESULTS: No differences between groups were noted with respect to clinicopathologic features; WBI patients demonstrated a trend for slightly larger tumors (1.3 vs. 1.1 cm, P = .06). At 10 years, no differences were noted with respect to rates of ipsilateral breast tumor recurrence (4% vs. 4%, P = .11), regional recurrence (1% vs. 1%, P = .20), contralateral breast failure (9% vs. 3%, P = .06), or distant metastases (3% vs. 6%, P = .47) for WBI and APBI, respectively. In addition, 10-year disease-free survival (93% vs. 91%, P = .10) and overall survival (83% vs. 75%, P = .34) were similar. Long-term cosmesis was good to excellent in 94% of WBI patients versus 95% of APBI patients (P = .78). CONCLUSIONS: At 10 years, no differences in recurrence or survival were found between patients undergoing WBI or brachytherapy-based APBI.

Department of Pathology

Human organic anion transporter 1 (hOAT1), expressed at the basolateral membrane of kidney proximal tubule cells, mediates the active renal secretion of a diverse array of clinically important drugs, including anti-human immunodeficiency virus therapeutics, antitumor drugs, antibiotics, antihypertensives, and anti-inflammatories. We have previously demonstrated that posttranslational modification of hOAT1 by ubiquitination is an important mechanism for the regulation of this transporter. The present study aimed at identifying the ubiquitin ligase for hOAT1 and its mechanism of action. We showed that overexpression of neural precursor cell expressed, developmentally downregulated (Nedd4)-1, an E3 ubiquitin ligase, enhanced hOAT1 ubiquitination,
decreased hOAT1 expression at the cell surface, and inhibited hOAT1 transport activity. In contrast, overexpression of the ubiquitin ligase-dead mutant Nedd4-1/C867S was without effects on hOAT1. Furthermore, knockdown of endogenously expressed Nedd4-1 by Nedd4-1-specific small interfering RNA reduced hOAT1 ubiquitination. Immunoprecipitation experiments in cultured cells and rat kidney slices and immunofluorescence experiments in rat kidney slices showed that there was a physical interaction between OAT1 and Nedd4-1. Nedd4-1 contains four protein–protein interacting WW domains. When these WW domains were inactivated by mutating two amino acid residues in each of the four WW domains (Mut-WW1: V210W/H212G, Mut-WW2: V367W/H369G, Mut-WW3: I440W/H442G, and Mut-WW4: I492W/H494G, respectively), only Mut-WW2 and Mut-WW3 significantly lost their ability to bind and to ubiquitinate hOAT1. As a result, Mut-WW2 and Mut-WW3 were unable to suppress hOAT1-mediated transport as effectively as wild-type Nedd4-1. In conclusion, this is the first demonstration that Nedd4-1 regulates hOAT1 ubiquitination, expression, and transport activity through its WW2 and WW3 domains. © 2016 The American Physiological Society.


Department of Internal Medicine

Background: Multi-gene panels are widely available for assessing hereditary cancer risk in high risk individuals. Due to the use of these panels, many genetic mutations other than BRCA 1 or 2 can be detected which can potentially affect management. This study presents the results of multi-gene panel testing performed at Beaumont Health System. Methods: All patients who underwent multi-gene panel testing at Beaumont Health System between November 1, 2012 and January 15, 2015 were included in this study. This cohort consisted of patients who met criteria for genetic testing due to personal or family history. All patients received comprehensive pre and post-test genetic counseling. The panels ranged from 5 to 43 genes associated with risk for breast and other cancers. Results: 653 multi-gene panel tests were performed. The majority of these consisted of either a 5 gene high risk breast panel (25%), an 18 gene moderate to high risk breast panel (21%), or a 9 gene high risk breast and gynecologic panel (17%). 184 variants of undetermined significance (VUS) were identified with a pooled VUS rate of 28%. Among the commonly used panels, there was a positive correlation between VUS rate and the number of genes included in the panel (r = 0.86, p = 0.01, Range 6% to 70%). A pathogenic mutation was identified in one or more genes in 65 (10%) panels for a total of 67 mutations. Of these, 17 mutations were in BRCA1 or BRCA2 gene. Fifty non-BRCA deleterious mutations were identified with the following frequencies: CHEK2(12), MUTYH(7 monoallelic, 1 biallelic), TP53(4), PTEN(4), ATM(4), MSH6(3), PALB2(3), MSH2(2), CDH1(2), APC(2), NF1(2), BARD1(2), MLH1(1) and PMS2(1). Of these non-BRCA mutations, 41(82%) had a significant impact on management. Conclusions: Our study demonstrates that multi-gene panel testing identifies several genes that can impact management and would likely not have been discovered by pedigree analysis alone. However, this added detection is associated with a higher VUS rate, especially using larger panels. Further research is needed to better define the role of multi-gene panel testing in high risk patients, with a focus on choosing appropriate genes, understanding the magnitude of cancer risk and delineating impact on management.


Department of Radiation Oncology


Department of Radiation Oncology


Department of Urology

Hypothesis/aims of study Long-term ketamine abuse results in severely inflamed bladder and intractable bladder pain. Currently there is no guideline for clinician to follow how to manage patients with ketamine cystitis (KC). This study analyzed the KC patient characteristics between who received conservative
management and augmentation enterocystoplasty (AE). Study design, materials and methods A total of 53 patients with chronic ketamine abuse and lower urinary tract symptoms were included in this study. All of the patients have been initially treated conservatively but fail. They were admitted for detailed urological examinations. Patients were classified according to their maximal bladder capacity (MBC). The patients with extremely small MBC (<100 mL) with or without upper urinary tract damage and very small MBC with upper urinary tract damage were recommended to receive AE. The patient characteristics and treatment outcome are compared between patients with AE and conservative treatment. Results Among them, 28 patients underwent AE and 25 were managed with conservative treatment. The only significant difference between groups was more patients with urgency urinary incontinence underwent AE. Patients underwent AE had significantly smaller MBC, thicker bladder wall, and higher incidence of vesicoureteral reflux. Patients underwent AE reported a good outcome. Most of patients received conservative treatment had a fair result. Interpretation of results The results of this study revealed that between KC patients undergoing conservative treatment and AE, the bladder capacity and upper urinary tract damage are two major factors. Cessation of ketamine use is the mainstay of control lower urinary tract symptoms in KC patients. However, for the patients who already developed a contracted bladder with extremely small bladder capacity (<100 mL) or very small capacity (100-300 mL) with irreversible urinary tract change such as thickened bladder wall and hydronephrosis, partial cystectomy and AE seems necessary for early restoration of a normal lower urinary tract function. The treatment outcome of AE is better than patients with conservative treatment. However, education and absolute cessation of ketamine use is still strongly recommended after AE. Concluding message KC patients who already developed a contracted bladder with extremely small bladder capacity (<300 mL) with irreversible urinary tract change, partial cystectomy and AE seems necessary for early restoration of a normal lower urinary tract function. The treatment outcome of AE is better than patients with conservative treatment. (Table presented).


Full-Text

Department of Ophthalmology

BACKGROUND AND OBJECTIVE: The authors report the technique of using the 27-gauge (G) vitreous cutter through 25-G valved cannulas to allow hybrid instrumentation of both gauges. PATIENTS AND METHODS: Vitrectomy is initiated with standard placement of 25-G valved cannulas, followed by insertion of a 27-G vitreous cutter through the 25-G cannulas. RESULTS: The hybrid procedure emphasizes the advantages of both platforms: The 25-G cutter is more efficient for core vitrectomy and is more rigid to facilitate peripheral vitrectomy; the 25-G platform enjoys a wider armamentarium of instrumentation options; and the smaller profile of the 27-G cutter can be maneuvered more easily into tight surgical planes to act analogous to vertical scissors, with the added benefits of aspiration and spatula-like features. The authors illustrate this technique in three cases: diabetic tractional retinal detachment with dense plaques, posterior stage 4B retinopathy of prematurity, and sutureless scleral fixation of an intraocular lens. CONCLUSIONS: Hybrid use of the 25-G and 27-G platforms offers greater versatility for the management of complex vitreoretinal conditions. © 2016, Slack Incorporated. All rights reserved.


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Department of Ophthalmology


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Department of Ophthalmology
Background The state of the art for correcting velopharyngeal insufficiency (VPI) is a surgical procedure which is customized according to findings on imaging procedures: multiplanar videofluoroscopy (MPVF) and flexible videonasopharyngoscopy (FVNP). The use of MPVF has been challenged because of the potential risk of using ionizing radiation, especially in children. Objective To study whether using a protocol for performing MPVF can effectively decrease radiation dose in patients with VPI while providing useful information for planning surgical correction of VPI in combination with FVNP. The methodology used for performing the imaging procedures is described as well as the effectiveness of the surgical procedure. Material and methods Eighty-nine patients (Age range = 3–17 years; median = 5.5 years) with VPI resulting from multiple etiologies were studied. All patients underwent MPVF and FVNP for planning surgical correction of VPI. Radiation dosage data in each case was recorded. Forty of the 89 patients also completed a postoperative evaluation. Eleven out of the remaining 49 patients have not completed a postoperative evaluation and 38 patients are still pending surgical correction. Results Radiation dosage ranged from 1.00 to 8.75 miliSieverts (mSv); Mean = 2.88 mSv; SD = 1.575 mSv. Preoperative nasometry demonstrated mean nasalance ranging from 41%–95%; Mean = 72.30; SD = 4.54. Postoperatively mean nasalance was within normal limits in 36 (90%) out of 40 cases, ranging from 21% to 35%; Mean = 28.10; SD = 5.40. Nasal emission was eliminated postoperatively in all cases. Conclusion MPVF provides useful information for planning the surgical procedure aimed at correcting VPI. The combination of MPVF and FVNP is a reliable procedure for assessing velopharyngeal closure and to surgically correcting VPI with a highly successful outcome.


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Department of Internal Medicine

Background Despite the development of prognostic factors for stratification models in AML patients, treatment response in individual patient has not been predicted accurately. Early assessment of individual response is of great practical significance in determining the timing of interim bone marrow biopsy and guide further chemotherapy. Our study investigates whether the timing of circulating blasts (CBs) clearance during induction therapy can predict treatment response in AML patients. Methods: We retrospectively reviewed the charts of 59 AML patients who received standard cytarabine and anthracycline regimen during induction between January, 2000 - 2011 at William Beaumont Health System. Patients with acute promyelocytic leukemia or history of myelodysplastic syndrome were excluded. AML is considered refractory if morphological evaluation, flow cytometry or cytogenetic study was positive in the post induction bone marrow results. Response to induction therapy was assessed according to Cancer and Leukemia Group B criteria as complete remission versus treatment failure. Results: We noted that 46 of 59 patients (77.9%) showed CBs at the time of diagnosis. During the induction therapy, CBs clearance occurred within 7 days (early clearance) in 31 among these 46 patients. The remaining 13 patients had CBs persistent more than 7 days (delayed clearance). The frequency of treatment failure was significant higher in patients with delayed clearance comparing to those with early clearance (93.3% vs 48.3%, p = 0.0033). There were no statistically significant difference in treatment response among cytogenetic risk groups, nor among age groups (60 years and older vs. younger than 60). Absence of peripheral blasts at diagnosis was not associated with superior complete remission rate comparing to group with early blast clearance (53.8% vs 51.6%, p > 0.05). Conclusions: Persistent peripheral blasts more than 7 days during standard induction therapy is associated with higher induction failure rates, regardless of cytogenetic risks and age. Clearance of CBs can be used as an independant predictor of treatment response to induction chemotherapy.


Department of Orthopedic Surgery


As diagnosis and treatment of cancer is improving, medical and social issues related to cancer survivorship are becoming more prevalent. Hemorrhagic cystitis (HC), a rare but serious disease that may affect patients after pelvic radiation or systemic chemotherapy, has significant unmet medical needs. Although no definitive treatment is currently available, various interventions are employed for HC. Effects of nonsurgical treatments for HC are of modest success and studies aiming to control radiation-induced bladder symptoms are lacking. In this review, we present current and advanced therapeutic strategies for HC to help cancer survivors deal with long-term urologic health issues.