

## Henry Ford Health System Publication List - March 2010

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You can access this page at <http://www.henryfordconnect.com/sliden.cfm?id=436>.

### **Biostatistics & Research Epidemiology**

Hensley Alford, S., C. M. McBride, R. J. Reid, E. B. Larson, A. D. Baxevanis and L. C. Brody (2010). "Participation in Genetic Testing Research Varies by Social Group." Public Health Genomics **Epub Ahead of Print**. [PDF Full-Text](#)

Henry Ford Hospital, Detroit, Mich., USA.

Background: Advances in technology have made individual access to personal genetic information foreseeable in the near future. Policy makers and the media forecast that the ready availability of personal genetic profiles would benefit both the individual and the health care system by improving outcomes and decreasing cost. However, there is a significant gap between having access to genetic data and either wanting or understanding the information it provides. Objective: Our primary aim was to evaluate, using a population-based sample of healthy adults, whether gender, race and education status influences interest and participation in a multiplex genetic susceptibility test. Methods: Healthy, insured individuals, 25-40 years of age, were approached via a large, integrated health system in which primary and specialty care is available. Study participants were offered personalized genetic risk information on 8 common chronic health conditions. Social groups historically known not to participate in genetic research (men, African Americans and those from lower education neighborhoods) were oversampled. We describe the recruitment outcomes and testing decisions of these social groups. Results: We found that even among those with access to health care, African Americans were less likely to participate in the multiplex genetic susceptibility test, while those from higher education neighborhoods were more likely to participate. Conclusions: Our results suggest that large social groups will likely be underrepresented in research in personalized genomics even when robust population-based recruitment strategies are employed.

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### **Biostatitics & Research Epidemiology**

Divine, G., A. Kapke, S. Havstad and C. L. Joseph (2010). "Exemplary data set sample size calculation for Wilcoxon-Mann-Whitney tests." Stat Med **29**(1): 108-15. 2796701. [PDF Full-Text](#)

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Zhao, Rahardja and Qu consider sample size calculation for Wilcoxon-Mann-Whitney (WMW) tests for data with ties, and present a straightforward formula. We observe that the 'exemplary data set' approach, usually applied in more complex situations, has a

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close relationship to the Zhao-Rahardja-Qu method for WMW sample size estimation and they are asymptotically equivalent. Therefore, the exemplary data set approach can be used to easily obtain estimates similar to those that the closed formula gives. We illustrate application of both methods for a WMW sample size estimation example, and also extend the simulation study presented by Zhao et al. We find that the Zhao-Rahardja-Qu formula (and by extension the exemplary data set method) can give estimates just as accurate as those obtained using either the Kolassa approach (via nQuery Advisor) or the O'Brien-Castelloe approach (via SAS 9.2 PROC POWER), for 1:1 and 1:2 allocation ratios. However, the latter two methods can be more accurate for a ratio of 1:4 or 1:19. Finally, we note the general utility of the exemplary data set approach for sample size estimation, even in other situations where closed-form sample size formulae exist.

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### **Bone & Joint Center**

Morandi, M., T. Banka, G. P. Gaiarsa, S. T. Guthrie, J. Khalil, J. Hoegler and B. G. Lindeque (2010). "Intramedullary nailing of tibial fractures: review of surgical techniques and description of a percutaneous lateral suprapatellar approach." *Orthopedics* **33**(3): 172-9.

[Article Request Form](#)

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### **Bone & Joint Center**

Shen, J., M. Yang, D. Ju, H. Jiang, J. P. Zheng, Z. Xu and L. Li (2010). "Disruption of SM22 Promotes Inflammation After Artery Injury via Nuclear Factor  $\{\kappa\}$ B Activation." *Circ Res* **Epub Ahead of Print**. [PDF Full-Text](#)

Department of Internal Medicine, Center for Molecular Medicine and Genetics, and Cardiovascular Research Institute, Wayne State University; and Bone and Joint Center, Henry Ford Hospital, Detroit, Mich.

Rationale: SM22 (or transgelin), an actin-binding protein abundant in vascular smooth muscle cells (VSMCs), is downregulated in atherosclerosis, aneurysm and various cancers. Abolishing SM22 in apolipoprotein E knockout mice accelerates atherogenesis. However, it is unclear whether SM22 disruption independently promotes arterial inflammation. Objective: To investigate whether SM22 disruption directly promotes inflammation on arterial injury and to characterize the underlying mechanisms. Methods and Results: Using carotid denudation as an artery injury model, we showed that Sm22 knockout (Sm22<sup>-/-</sup>) mice developed enhanced inflammatory responses with higher induction of proinflammatory genes, including Vcam1, Icam1, Cx3cl1, Ccl2, and Ptgs2. Higher expression of these genes was confirmed in primary, Sm22<sup>-/-</sup> VSMCs and in PAC1 cells after Sm22 knockdown, whereas SM22 recapitulation in primary Sm22<sup>-/-</sup> VSMCs decreased their expression. NF-kappaB pathways were prominently activated in both injured carotids of Sm22<sup>-/-</sup> mice and in PAC1 cells after Sm22 knockdown and may mediate upregulation of these proinflammatory genes. As a NF-kappaB activator, reactive oxygen species (ROS) increased in primary Sm22<sup>-/-</sup> VSMCs and in PAC1 cells after Sm22 knockdown. ROS scavengers blocked NF-kappaB activation and induction of proinflammatory genes. Furthermore, Sm22 knockdown increased Sod2 expression and activated p47phox, reflecting contributions of mitochondria and NADPH oxidase to the augmented ROS production; this may result from actin and microtubule cytoskeletal remodeling. Conclusions: Our findings show that SM22 downregulation in VSMCs can independently promote arterial inflammation through activation of ROS-mediated NF-kappaB pathways. This study provides initial evidence linking VSMC cytoskeleton remodeling with arterial inflammation.

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### **Cardiology**

Felker, G. M., P. S. Pang, K. F. Adams, J. G. F. Cleland, G. Cotter, K. Dickstein, G. S. Filippatos, G. C. Fonarow, B. H. Greenberg, A. F. Hernandez, S. Khan, M. Komajda, M. A. Konstam, P. P. Liu, A. P. Maggioni, B. M. Massie, J. J. McMurray, M. Mehra, M. Metra, J. O'Connell, C. M. O'Connor, I. L. Pina, P. Ponikowski, H. N. Sabbah, J. R. Teerlink, J. E. Udelson, C. W. Yancy, F. Zannad and M. Gheorghiade (2010). "Clinical Trials of

Pharmacological Therapies in Acute Heart Failure Syndromes Lessons Learned and Directions Forward." Circulation-Heart Failure **3**(2): 314-325. [PDF Full-Text](#)

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## Cardiology

Hudson, M., A. Greenbaum, L. Brenton, C. M. Gibson, R. Siegel, L. R. Reeves, M. F. Sala, G. McKendall, J. Blugermann, D. Echt, E. M. Ohman and W. D. Weaver (2010).

"Adjunctive transcutaneous ultrasound with thrombolysis: results of the PLUS (Perfusion by ThromboLytic and UltraSound) trial." JACC Cardiovasc Interv **3**(3): 352-9. [Article Request Form](#)

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**OBJECTIVES:** We investigated whether transcutaneous ultrasound (TUS) augments coronary thrombolysis and achieves higher rates of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 and ST-segment resolution in patients with ST-segment elevation myocardial infarction (STEMI). **BACKGROUND:** In animal coronary and peripheral artery thrombosis models, low-frequency TUS enhances and accelerates thrombolysis. **METHODS:** In a double-blind, randomized, controlled international clinical trial, 396 patients with STEMI < or =6 h were randomized to thrombolysis alone or thrombolysis plus TUS. The 60 minute TIMI flow grade, ST-segment resolution (primary end points) and other angiographic, electrocardiographic, and clinical outcomes were compared between treatment groups. **RESULTS:** The trial was halted after Safety and Efficacy Monitoring Committee interim analysis that demonstrated lack of treatment efficacy. In total, 360 patients were evaluable for angiographic, electrocardiographic, or clinical end points. Sixty minutes after thrombolytic administration, the proportion of patients achieving TIMI flow grade 3 did not differ between TUS and control groups (40.7% vs. 48.5%, respectively;  $p = 0.10$ ). Achievement of >50% ST-segment resolution at 60 min did not differ between TUS and control groups (53.2% vs. 50.0%;  $p = 0.93$ ). Thirty-day mortality and composite clinical events-death, reinfarction, recurrent ischemia, stroke, major bleed, left ventricular rupture (9.7 % vs. 10.2%;  $p = 0.88$ )-did not differ between TUS and control patients. **CONCLUSIONS:** Thrombolysis plus TUS failed to improve 60-min TIMI flow grade or ST-segment resolution versus thrombolysis alone.

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## Cardiology

Keteyian, S. J., I. L. Pina, B. A. Hibner and J. L. Fleg (2010). "Clinical role of exercise training in the management of patients with chronic heart failure." J Cardiopulm Rehabil Prev **30**(2): 67-76. [PDF Full-Text](#)

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Prior exercise research and the recently completed HF-ACTION (Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training) trial indicate that regular exercise represents an effective therapy in the management of patients with stable chronic heart failure (HF) due to left ventricular systolic dysfunction. This review summarizes the results from these studies and provides a guide for prescribing exercise. Regular aerobic-type exercise training improves exercise capacity; does not worsen and may, in fact, mildly improve cardiac function; and partially improves other physiological abnormalities that develop because of chronic HF (eg, autonomic and skeletal muscle function). Regular exercise is safe, improves health status, and modestly reduces (approximately 15%) combined risk for cardiovascular death or HF-related hospitalization. Even greater physiological and clinical benefits appear likely in patients with HF who adhere to a higher volume of exercise (eg, 6 MET-hr per week). The exercise regimen should include an aerobic-type activity performed at least 30 minutes, 5 or more days per week, and at an intensity approximating 55% to 80% of heart rate reserve. Resistance training should be considered for patients who first demonstrate they are able to tolerate aerobic exercise training. Common to other interventions that also rely on human behavior, long-term adherence to exercise in patients with HF remains a challenge and requires additional research to determine strategies aimed at improving compliance. Areas of needed research include identifying which patient subgroup(s) benefits the most and determination of the optimal intensity, duration, and frequency of exercise needed to maximize clinical benefits and attenuate fatigue.

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## Center for Health Promotion & Disease Prevention

Milberger, S. M., R. M. Davis and A. L. Holm (2009). "Pet owners' attitudes and behaviours related to smoking and second-hand smoke: a pilot study." Tob Control **18**(2): 156-8. [PDF Full-Text](#)

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**BACKGROUND:** Although research indicates that second-hand smoke (SHS) harms both human and animal health, data on the percentage of pet owners who smoke or allow smoking in their homes are not readily available. **OBJECTIVE:** To investigate pet owners' smoking behaviour and policies on smoking in their homes, and the potential for educational interventions to motivate change in pet owners' smoking behaviour. **METHODS:** A web-based survey was used with 3293 adult pet owners. The main outcome measures were smoking behaviour of pet owners and their cohabitants; policies on smoking in pet owners' homes; and impact of information about the dangers of pet exposure to SHS on pet owners' smoking intentions. **RESULTS:** Of respondents, 21% were current smokers and 27% of participants lived with at least one smoker. Pet owners who smoke reported that information on the dangers of pet exposure to SHS would motivate them to try to quit smoking (28.4%) and ask the people with whom they live to quit smoking (8.7%) or not to smoke indoors (14.2%). Moreover, non-smoking pet owners who live with smokers said that they would ask the people with whom they live to quit (16.4%) or not smoke indoors (24.2%) if given this information. About 40% of current smokers and 24% of non-smokers living with smokers indicated that they would be interested in receiving information on smoking, quitting, or SHS. **CONCLUSIONS:** Educational campaigns informing pet owners of the risks of SHS exposure for pets could motivate some owners to quit smoking. It could also motivate these owners and non-smoking owners who cohabit with smokers make their homes smoke-free.

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## Dermatology

Desai, S., B. H. Mahmoud, A. C. Bhatia and I. H. Hamzavi (2010). "Paradoxical Hypertrichosis After Laser Therapy: A Review." Dermatologic Surgery **36**(3): 291-298. [PDF Full-Text](#)

[Desai, Shraddha; Bhatia, Ashish C.] DuPage Med Grp, Inst Dermatol, Naperville, IL 60563 USA. [Desai, Shraddha] Loyola Univ, Dept Dermatol, Maywood, IL 60153 USA. [Mahmoud, Bassel H.; Hamzavi, Iltefat H.] Henry Ford Hosp, Dept Dermatol, Detroit, MI 48202 USA. [Bhatia, Ashish C.] Northwestern Univ, Dept Dermatol, Chicago, IL 60611 USA.  
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BACKGROUND Laser hair removal is a safe and effective procedure for the treatment of unwanted body hair but is not exempt from side effects. A rare but significant adverse effect with this treatment modality is paradoxical hypertrichosis. OBJECTIVE To evaluate the potential etiologies, risk factors, related laser types, and treatment options for the development of excess hair after laser therapy. MATERIALS AND METHODS An analysis of previously published case studies and review articles along with our own experience was used to gather information regarding this phenomenon. RESULTS Paradoxical hypertrichosis has a low incidence, ranging from 0.6% to 10%, and most commonly occurs on the face and neck. All laser and light sources have the potential to cause hair induction, especially in individuals with darker skin types (III-VI); with dark, thick hair; and with underlying hormonal conditions. Possible causes include the effect of inflammatory mediators and subtherapeutic thermal injury causing induction of the hair cycle. Treatment for paradoxical hypertrichosis is laser therapy of the affected area. CONCLUSIONS Paradoxical hypertrichosis is a rare side effect of laser hair removal; the pathogenesis of this event remains widely unknown. We recommend further large-scale studies to investigate this effect. The authors have indicated no significant interest with commercial supporters.

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### **Dermatology**

Gold, L. F. S. (2009). "Calcitriol Ointment: Optimizing Psoriasis Therapy." Journal of Drugs in Dermatology 8(8): S23-S27. [Article Request Form](#)

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The topical vitamin D-3 modulator calcitriol, the naturally occurring active form of vitamin D-3, has long been used for topical psoriasis therapy in Europe and other countries and was recently approved in the United States (U.S.) for the treatment of plaque psoriasis. In vehicle-controlled clinical trials, calcitriol 3 mu g/g ointment has been shown to significantly improve the symptoms of psoriasis with a low incidence of adverse effects and without affecting calcium homeostasis, even when applied continuously for up to one year. A number of studies have examined the efficacy and safety of calcitriol ointment in combination therapy regimens that also included topical corticosteroid therapy or ultraviolet B (UVB) phototherapy. Calcitriol 3 mu g/g ointment is a new option that provides flexibility for use in a variety of psoriasis treatment regimens. According to guidelines developed by the American Academy of Dermatology (AAD), the goals of psoriasis treatment are to produce durable remission of psoriasis symptoms, to achieve "substantial" clearing with the possibility of complete clearing, to maintain the initial benefits of therapy, and to minimize the risk of adverse events.(1) Topical medications are the most commonly used treatments for psoriasis in the U.S.(2) and are important in meeting the goals of psoriasis therapy. These agents offer high response rates with generally favorable safety and tolerability profiles and are useful for both acute treatment and long-term maintenance. Topical medications are used by approximately 85% of patients with psoriasis.(3)

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### **Dermatology**

Gold, L. S., A. Cruz, L. Eichenfield, J. Tan, J. Jorizzo, N. Kerrouche and J. C. Dhuin (2010). "Effective and Safe Combination Therapy for Severe Acne Vulgaris: A Randomized, Vehicle-Controlled, Double.-blind Study of Adapalene 0.1%-Benzoyl Peroxide 2.5% Fixed-Dose Combination Gel With Doxycycline Hyclate 100 mg." Cutis 85(2): 94-104. [PDF Full-Text \(ID=sladenjournals@hfhs.org / PW=frank\)](#)

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There is a paucity of treatment options for severe acne vulgaris aside from oral isotretinoin. This randomized, vehicle-controlled, multicenter, double-blind study evaluated the efficacy and safety of combination therapy using adapalene 0.1%- benzoyl peroxide 2.5% (A/BPO) fixed-dose combination gel with doxycycline hyclate 100 mg in the treatment of severe acne vulgaris. A total of 459 participants were randomized in a 1:1 ratio to receive oral doxycycline hyclate 100 mg once daily and either A/BPO or vehicle once daily for 12 weeks. Efficacy in the A/BPO with doxycycline group was demonstrated as early as week 2 compared with the vehicle arm for total, inflammatory, and noninflammatory lesions (all  $P < .005$ ). At week 12, this combination was superior to vehicle with doxycycline in reducing total, inflammatory, and noninflammatory lesion counts (an added incremental benefit of 23%, 24%, and 21%, respectively), as well as for global success and overall participant satisfaction (all  $P < .001$ ). Digital UV fluorescence photography demonstrated a rapid reduction in *Propionibacterium acnes* in the A/BPO with doxycycline group, particularly within the first 4 weeks. These findings provide evidence on the efficacy of combining A/BPO and the oral antibiotic doxycycline in the treatment of severe acne vulgaris. *Cutis*. 2010;85:94-104.

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## Dermatology

Li, C. G., L. Han, A. M. Levin, H. D. Song, S. L. Yan, Y. Wang, Y. L. Wang, D. M. Meng, S. Lv, Y. Ji, X. C. Xu, X. X. Liu, Y. G. Wang, L. Zhou, Z. M. Miao and Q. S. Mi (2010). "Multiple single nucleotide polymorphisms in the human urate transporter 1 (hURAT1) gene are associated with hyperuricaemia in Han Chinese." *Journal of Medical Genetics* **47**(3): 204-210. [PDF Full-Text](#)

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**Objective** The present study investigated whether single nucleotide polymorphisms (SNPs) in the human urate transporter 1 (hURAT1) gene are associated with primary hyperuricaemia (HUA) in Han Chinese people. **Methods** A total of 538 subjects (215 cases and 323 control subjects) were recruited from Qingdao, China. SNPs in potentially functional regions of the gene were identified and genotypes determined by direct sequencing. Association analyses were conducted using Fisher's exact test and logistic regression assuming a genotype model. **Results** By sequencing the promoter, 10 exons, and the exon-intron junctions of the hURAT1 gene, 14 SNPs were identified. Two of the SNPs identified were associated with susceptibility to HUA. The first was a rare intron 3 (11 G → A) SNP ( $p = 0.0005$ ), where carriers of the 'A' allele had a 3.4-fold (95% CI 1.67 to 6.93) increased risk of HUA. The second was a common exon 8 (T1309C) SNP (rs7932775), where carriers of one and two 'C' alleles had respective fold increased risks of 1.64 (95% CI 1.07 to 2.52) and 2.32 (95% CI 1.37 to 3.95). These SNPs had a joint additive effect of risk of HUA, with those individuals carrying at least one 'A' allele at the intron 3 SNP and two 'C' alleles at rs7932775 having a 5.88-fold (95% CI 1.25 to 15.57) increased risk of HUA in comparison to those with no risk alleles. **Conclusion** In conjunction with other studies, our results suggest that there are multiple genetic variants within or near hURAT1 that are associated with susceptibility to HUA in Han Chinese, including a novel SNP located in intron 3.

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## Dermatology

Mahmoud, B. H., E. Tierney, C. L. Hexsel, J. Pui, D. M. Ozog and I. H. Hamzavi (2010). "Prospective controlled clinical and histopathologic study of hidradenitis suppurativa treated with the long-pulsed neodymium:yttrium-aluminium-garnet laser." *J Am Acad Dermatol* **62**(4): 637-45. [PDF Full-Text](#)

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**BACKGROUND:** Hidradenitis suppurativa (HS) is a chronic inflammatory disease involving the intertriginous areas. **OBJECTIVE:** We sought to conduct clinical and histopathologic evaluation of the efficacy of long-pulsed neodymium:yttrium-aluminium-garnet laser treatment for HS. **METHODS:** We conducted a prospective, randomized, right-left within-patient controlled trial for HS (n = 22). Four monthly laser sessions were performed. Disease activity was measured at baseline, and treatment response was assessed before each laser session and monthly for 2 months after the completion of laser treatment, using a modified scoring system based on Sartorius score. Histologic examination was performed at baseline, immediately after laser treatment, and at 1 and 4 weeks after treatment. A patient questionnaire was circulated on the last visit to assess patients' level of satisfaction. **RESULTS:** There was progressive improvement in disease activity, most significantly during the 4 months of treatment, which was maintained during the 2-month posttreatment follow-up period. Averaged over all anatomic sites, the percent improvement was 72.7% on the laser treated side, and 22.9% on the control side (P < .05). Histologic examination showed an initial acute neutrophilic infiltrate. Granulomatous inflammation was present on follow-up biopsy specimens 4 weeks later. An inflammatory infiltrate surrounded the hair shaft remnants, denoting destruction of hair follicles. **LIMITATIONS:** Small sample size was a limitation. **CONCLUSIONS:** Long-pulsed neodymium:yttrium-aluminium-garnet laser, together with topical benzoyl peroxide and clindamycin, is significantly more effective than topical benzoyl peroxide and clindamycin alone for the treatment of HS. Preliminary review of histopathology suggests the mechanism of action is destruction of the hair follicle. The overall success of the treatment in both clearing pre-existing lesions and preventing new eruptions, coupled with high patient satisfaction, makes the neodymium:yttrium-aluminium-garnet laser a promising treatment advance for this highly disabling condition.

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## Dermatology

Zhao, X. H., X. L. He, X. L. Han, Y. Yu, F. Ye, Y. Chen, T. Hoang, X. M. Xu, Q. S. Mi, M. Xin, F. Wang, B. Appel and Q. R. Lu (2010). "MicroRNA-Mediated Control of Oligodendrocyte Differentiation." *Neuron* **65**(5): 612-626. [PDF Full-Text](#)

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MicroRNAs (miRNAs) regulate various biological processes, but evidence for miRNAs that control the differentiation program of specific neural cell types has been elusive. To determine the role of miRNAs in the formation of myelinating oligodendrocytes, we selectively deleted a miRNA-processing enzyme, Dicer1, in oligodendrocyte lineage cells. Mice lacking Dicer1 display severe myelinating deficits despite an expansion of the oligodendrocyte progenitor pool. To search for miRNAs responsible for the induction of oligodendrocyte maturation, we identified miR-219 and miR-338 as oligodendrocyte-specific miRNAs in spinal cord. Overexpression of these miRNAs is sufficient to promote oligodendrocyte differentiation. Additionally, blockage of these miRNA activities in oligodendrocyte precursor culture and knockdown of miR-219 in zebrafish inhibit oligodendrocyte maturation. miR-219 and miR-338 function in part by directly repressing negative regulators of oligodendrocyte differentiation, including transcription factors Sox6 and Hes5. These findings illustrate that miRNAs are important regulators of oligodendrocyte differentiation, providing new targets for myelin repair.

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## Diagnostic Radiology

Arbab, A. S., B. Janic, K. Jafari-Khouzani, A. S. Iskander, S. Kumar, N. R. Varma, R. A. Knight, H. Soltanian-Zadeh, S. L. Brown and J. A. Frank (2010). "Differentiation of glioma and radiation injury in rats using in vitro produce magnetically labeled cytotoxic T-cells and MRI." *PLoS One* **5**(2): e9365. 2829084. [PDF Full-Text](#)

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**BACKGROUND:** A limitation with current imaging strategies of recurrent glioma undergoing radiotherapy is that tumor and radiation injury cannot be differentiated with post contrast CT or MRI, or with PET or other more complex parametric analyses of MRI data. We propose to address the imaging limitation building on emerging evidence indicating that effective therapy for recurrent glioma can be attained by sensitized T-cells following vaccination of primed dendritic cells (DCs). The purpose of this study was to determine whether cord blood T-cells can be sensitized against glioma cells (U-251) and if these sensitized cytotoxic T-cells (CTLs) can be used as cellular magnetic resonance imaging probes to identify and differentiate glioma from radiation necrosis in rodent models. **METHODOLOGY/PRINCIPAL FINDINGS:** Cord blood T and CD14+ cells were collected. Isolated CD14+ cells were then converted to dendritic cells (DCs), primed with glioma cell lysate and used to sensitize T-cells. Phenotypical expression of the generated DCs were analyzed to determine the expression level of CD14, CD86, CD83 and HLA-DR. Cells positive for CD25, CD4, CD8 were determined in generated CTLs. Specificity of cytotoxicity of the generated CTLs was also determined by lactate dehydrogenase (LDH) release assay. Secondary proliferation capacity of magnetically labeled and unlabeled CTLs was also determined. Generated CTLs were magnetically labeled and intravenously injected into glioma bearing animals that underwent MRI on days 3 and 7 post- injection. CTLs were also administered to animals with focal radiation injury to determine whether these CTLs accumulated non-specifically to the injury sites. Multi-echo T2- and T2\*-weighted images were acquired and R2 and R2\* maps created. Our method produced functional, sensitized CTLs that specifically induced U251 cell death in vitro. Both labeled and unlabeled CTLs proliferated equally after the secondary stimulation. There were significantly higher CD25 positive cells ( $p = <0.006$ ) in CTLs. In addition, T2- and T2\*-weighted MR images showed increased low signal intensity areas in animals that received labeled CTLs as compared to the images from animals that received control cells. Histological analysis confirmed the presence of iron positive cells in sites corresponding to MRI low signal intensity regions. Significant differences ( $p = <0.001$ ) in tumor R2 and R2\* values were observed among the groups of animals. Animals with radiation injury exhibited neither MRI hypointense areas nor presence of iron positive cells. **CONCLUSION:** Our results indicate that T-cells can be effectively sensitized by in vitro methods and used as cellular probes to identify and differentiate glioma from radiation necrosis.

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### **Diagnostic Radiology**

Ghannad-Rezaie, M., H. Soltanian-Zadeh, H. Ying and M. Dong (2010). "Selection-Fusion Approach for Classification of Datasets with Missing Values." *Pattern Recognit* **43**(6): 2340-2350. 2832761. [Article Request Form](#)

Department of Diagnostic Radiology, Henry Ford Hospital, Detroit, MI 48202, USA.

This paper proposes a new approach based on missing value pattern discovery for classifying incomplete data. This approach is particularly designed for classification of datasets with a small number of samples and a high percentage of missing values where available missing value treatment approaches do not usually work well. Based on the pattern of the missing values, the proposed approach finds subsets of samples for which most of the features are available and trains a classifier for each subset. Then, it combines the outputs of the classifiers. Subset selection is translated into a clustering problem, allowing derivation of a mathematical framework for it. A trade off is established between the computational complexity (number of subsets) and the accuracy of the overall classifier. To deal with this trade off, a numerical criterion is proposed for the prediction of the overall performance. The proposed method is applied to seven datasets from the popular University of California, Irvine data mining archive and an epilepsy dataset from Henry Ford Hospital, Detroit, Michigan (total of eight datasets). Experimental results show that classification accuracy of the proposed method is superior to those of the widely used multiple imputations method and four other methods. They also show that the level of superiority depends on the pattern and percentage of missing values.

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### **Diagnostic Radiology**

Hosseini, M. S., B. N. Araabi and H. Soltanian-Zadeh (2010). "Pigment Melanin: Pattern for Iris Recognition." *IEEE Transactions on Instrumentation and Measurement* **59**(4): 792-804. [Article Request Form](#)

[Araabi, Babak N.; Soltanian-Zadeh, Hamid] Univ Tehran, Sch Elect & Comp Engn, Control & Intelligent Proc Ctr Excellence, Tehran 14395515, Iran. [Soltanian-Zadeh, Hamid] Henry Ford Hosp, Dept Radiol, Image Anal Lab, Detroit, MI 48202 USA.

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Recognition of iris based on visible light (VL) imaging is a difficult problem because of the light reflection from the cornea. Nonetheless, pigment melanin provides a rich feature source in VL, which is unavailable in near-infrared (NIR) imaging. This is due to the biological spectroscopy of eumelanin, a chemical not stimulated in NIR. In this case, a plausible solution to observe such patterns may be provided by an adaptive procedure using a variational technique on the image histogram. To describe the patterns, a shape analysis method is used to derive the feature code for each subject. An important question is how the melanin patterns, which are extracted from VL, are independent of the iris texture in NIR. With this question in mind, the present investigation proposes fusion of features extracted from NIR and VL to boost recognition performance. We have collected our own database (UTIRIS), consisting of both NIR and VL images of 158 eyes of 79 individuals. This investigation demonstrates that the proposed algorithm is highly sensitive to the patterns of chromophores and improves the iris recognition rate.

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### **Diagnostic Radiology**

Jain, R., J. Narang, P. M. Sundgren, D. Hearshen, S. Saksena, J. P. Rock, J. Gutierrez and T. Mikkelsen (2010). "Treatment induced necrosis versus recurrent/progressing brain tumor: going beyond the boundaries of conventional morphologic imaging." J Neurooncol **Epub Ahead of Print**. [PDF Full-Text](#)

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Brain tumor patients undergo various combinations therapies, leading to very complex and confusing imaging appearances on follow up MR imaging and hence, differentiating recurrent or progressing tumors from treatment induced necrosis or effects has always been a challenge in neuro-oncologic imaging. This particular topic has become more relevant these days because of the advent of newer anti-angiogenic and anti-neoplastic chemotherapeutic agents as well as use of salvage radiation therapy. Various clinically available functional imaging modalities can provide additional physiologic and metabolic information about the tumors which could be useful in identifying viable tumor from treatment induced necrosis and hence, can guide treatment planning. In this review we will discuss various functional neuro-imaging modalities, their advantages and limitations and also their utility in treatment planning.

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### **Diagnostic Radiology**

Jain, R., L. M. Scarpace, S. Ellika, R. Torcuator, L. R. Schultz, D. Hearshen and T. Mikkelsen (2010). "Imaging response criteria for recurrent gliomas treated with bevacizumab: role of diffusion weighted imaging as an imaging biomarker." J Neurooncol **96(3): 423-31**. [PDF Full-Text](#)

Henry Ford Hospital, Detroit, MI, USA. [rajanj@rad.hfh.edu](mailto:rajanj@rad.hfh.edu)

The purpose of this study was to assess the usefulness of diffusion weighted imaging as an additional imaging biomarker for treatment response in recurrent/progressive malignant gliomas treated with bevacizumab alone or in combination with other chemotherapeutic agents. Twenty patients treated with bevacizumab alone or concurrent chemotherapy were followed up with serial MR imaging. Volume and ADC values of contrast enhancing lesion (CEL(vol), CEL(ADC)) and also of non-enhancing lesion (NEL(vol), NEL(ADC)) were obtained. CEL(vol) showed a progressive decrease in non-progressors with a median percentage change of -73.2% (P = 0.001) as compared to -33.4% for progressors by 1 year/last imaging (P = 0.382). NEL(vol) also showed a decrease in non-progressors on follow up imaging though only significant for 3 months follow up (P = 0.042). In progressors, CEL(vol) and NEL(vol) showed initial decrease followed by slight increase by 1 year/last imaging though not significant (P value of 0.382 and 0.46, respectively). CEL(ADC) and NEL(ADC) in non-progressors did not show any statistically significant change though there was slight trend for positive percent change especially for CEL(ADC) by 1 year/last imaging follow up study (P value of 0.077 and 0.339,

respectively). Progressors showed a progressive negative percent change of CEL(ADC) and NEL(ADC). In progressors, NEL(ADC) decreased at 6 weeks ( $P = 0.054$ ), 3 months ( $P = 0.023$ ) and 1 year/last ( $P = 0.078$ ) as compared to baseline study and was also statistically significant as compared to non-progressors at 6 weeks ( $P = 0.047$ ) and 3 months ( $P = 0.025$ ). CEL(ADC) and NEL(ADC) appear to follow different trends over time for non-progressors and progressors with a stable to slightly progressive increase in non-progressors and a progressive decrease in progressors, especially early on. These findings suggest that DWI may be used as an additional imaging biomarker for early treatment response.

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## Diagnostic Radiology

Way, T., H. P. Chan, L. Hadjiiski, B. Sahiner, A. Chughtai, T. K. Song, C. Poopat, J. Stojanovska, L. Frank, A. Attili, N. Bogot, P. N. Cascade and E. A. Kazerooni (2010).

"Computer-Aided Diagnosis of Lung Nodules on CT Scans: ROC Study of Its Effect on Radiologists' Performance." Academic Radiology **17**(3): 323-332. [Article Request Form](#)

[Way, Ted; Chan, Heang-Ping; Hadjiiski, Lubomir; Sahiner, Berkman; Chughtai, Aamer; Stojanovska, Jadranka; Frank, Luba; Attili, Anil; Bogot, Naama; Cascade, Philip N.; Kazerooni, Ella A.] Univ Michigan, Dept Radiol, Ann Arbor, MI 48109 USA. [Song, Thomas K.; Poopat, Chad] Henry Ford Hosp, Dept Radiol, Detroit, MI 48202 USA.

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Rationale and Objectives: The aim of this study was to evaluate the effect of computer-aided diagnosis (CAD) on radiologists' estimates of the likelihood of malignancy of lung nodules on computed tomographic (CT) imaging. Methods and Materials: A total of 256 lung nodules (124 malignant, 132 benign) were retrospectively collected from the thoracic CT scans of 152 patients. An automated CAD system was developed to characterize and provide malignancy ratings for lung nodules on CT volumetric images. An observer study was conducted using receiver-operating characteristic analysis to evaluate the effect of CAD on radiologists' characterization of lung nodules. Six fellowship-trained thoracic radiologists served as readers. The readers rated the likelihood of malignancy on a scale of 0% to 100% and recommended appropriate action first without CAD and then with CAD. The observer ratings were analyzed using the Dorfman-Berbaum-Metz multireader, multicase method. Results: The CAD system achieved a test area under the receiver-operating characteristic curve ( $A(z)$ ) of  $0.857 \pm 0.023$  using the perimeter, two nodule radii measures, two texture features, and two gradient field features. All six radiologists obtained improved performance with CAD. The average  $A(z)$  of the radiologists improved significantly ( $P < .01$ ) from 0.833 (range, 0.817-0.847) to 0.853 (range, 0.834-0.887). Conclusion: CAD has the potential to increase radiologists' accuracy in assessing the likelihood of malignancy of lung nodules on CT imaging.

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## Emergency Medicine

Nguyen, H. B., M. Loomba, J. J. Yang, G. Jacobsen, K. Shah, R. M. Otero, A. Suarez, H. Parekh, A. Jaehne and E. P. Rivers (2010). "Early lactate clearance is associated with

biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock." Journal of Inflammation-London **7**. [PDF Full-Text](#)

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Nguyen, HB, Loma Linda Univ, Dept Emergency Med, Loma Linda, CA 92350 USA. [hbryantn@yahoo.com](mailto:hbryantn@yahoo.com)

Background: Lactate clearance, a surrogate for the magnitude and duration of global tissue hypoxia, is used diagnostically, therapeutically and prognostically. This study examined the association of early lactate clearance with selected inflammatory, coagulation, apoptosis response biomarkers and organ dysfunction scores in severe sepsis and septic shock. Methods: Measurements of serum arterial lactate, biomarkers (interleukin-1 receptor antagonist, interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor-alpha, intercellular adhesion molecule-1, high mobility group box-1, D-Dimer and caspase-3), and organ dysfunction

scores (Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology Score II, Multiple Organ Dysfunction Score, and Sequential Organ Failure Assessment) were obtained in conjunction with a prospective, randomized study examining early goal-directed therapy in severe sepsis and septic shock patients presenting to the emergency department (ED). Lactate clearance was defined as the percent change in lactate levels after six hours from a baseline measurement in the ED. Results: Two-hundred and twenty patients, age 65.0 +/- 17.1 years, were examined, with an overall lactate clearance of 35.5 +/- 43.1% and in-hospital mortality rate of 35.0%. Patients were divided into four quartiles of lactate clearance, -24.3 +/- 42.3, 30.1 +/- 7.5, 53.4 +/- 6.6, and 75.1 +/- 7.1%, respectively ( $p < 0.01$ ). The mean levels of all biomarkers and organ dysfunction scores over 72 hours were significantly lower with higher lactate clearance quartiles ( $p < 0.01$ ). There was a significant decreased in-hospital, 28-day, and 60-day mortality in the higher lactate clearance quartiles ( $p < 0.01$ ). Conclusions: Early lactate clearance as a surrogate for the resolution of global tissue hypoxia is significantly associated with decreased levels of biomarkers, improvement in organ dysfunction and outcome in severe sepsis and septic shock.

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## Emergency Medicine

Nguyen, H. B., J. Oh, R. M. Otero, K. Burroughs, W. A. Wittlake and S. W. Corbett (2010). "Standardization of Severe Sepsis Management: A Survey of Methodologies in Academic and Community Settings." Journal of Emergency Medicine **38**(2): 122-132. [PDF Full-Text](#)

[Nguyen, H. Bryant] Loma Linda Univ, Med Ctr, Dept Emergency Med, Loma Linda, CA 92354 USA. [Nguyen, H. Bryant] Loma Linda Univ, Dept Med, Div Pulm & Crit Care Med, Loma Linda, CA 92354 USA. [Oh, Jason] Univ Maryland, Dept Emergency Med, Baltimore, MD 21201 USA. [Otero, Ronny M.] Henry Ford Hosp, Dept Emergency Med, Detroit, MI 48202 USA.

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Background: Evidence-based therapies for severe sepsis include early antibiotics, early goal-directed therapy, corticosteroids, recombinant human activated protein C, glucose control, and lung protective strategies. Objective: The objective of this study was to analyze methods, challenges, and outcomes observed by hospitals that implemented a hospital-wide sepsis management protocol incorporating evidence-based therapies. Methods: In a cross-sectional multi-center telephone survey over a 4-month period, clinicians (participants) responsible for developing a hospital sepsis protocol were questioned regarding its development and outcomes. Results: Participants completing surveys represented 40 hospitals (20 academic and 20 community). Twenty-seven percent of protocol champions were Emergency physicians or nurses. Sixty-three percent reported protocol development time of 6-12 months. Eighty-eight percent of participants reported protocol initiation in the Emergency Department. Three participants reported hiring a nurse educator to implement the protocol. Ninety-five percent of participants measure lactate as part of patient screening. Protocol therapies reported included early antibiotics (98% early goal directed-therapy (EGDT) (98%), corticosteroids (80% and activated protein C (73%). Contributions to success included having a protocol champion (85%) and sepsis education program (65%). Twenty-one participants had recorded patient-level data, totaling 2319 protocol patients, compared to 1719 non-protocol patients, with in-hospital mortality of 23% and 44%, respectively. Conclusions: Implementation of a sepsis management protocol incorporating evidence-based therapies can be accomplished in both academic and community hospitals, with minimal additional staffing. The presence of a protocol champion and education program is crucial to success, and may result in improved patient outcome. (C) 2010 Elsevier Inc.

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## Emergency Medicine

Rivers, E. P., V. Coba and M. Rudis (2009). "Standardized order sets for the treatment of severe sepsis and septic shock." Expert Rev Anti Infect Ther **7**(9): 1075-9. [Article Request Form](#)

Henry Ford Hospital, Department of Emergency Medicine, 2799 West Grand Boulevard, 270 Clara Ford Pavillion, Detroit, MI 48202, USA. [erivers1@hfhs.org](mailto:erivers1@hfhs.org)

Evaluation of: Thiel SW, Asghar MF, Micek ST, Reichley RM, Doherty JA, Kollef MH. Hospital-wide impact of standardized order set for the management of bacteremic severe sepsis. Crit. Care Med. 37(3), 819-824 (2009). Aggressive standardized diagnostic and therapeutic approaches to acute diseases such as acute

myocardial infarction, trauma and stroke have led to improved patient survival. A standardized order set for severe sepsis and septic shock represents a similar approach. In 2001, Rivers et al., using a standardized operating procedure to treat severe sepsis and septic shock, showed a relative risk reduction of 0.34 and absolute risk reduction of 16%, with a decrease in healthcare resource consumption for patients presenting to the emergency department. Since then, similar studies have shown similar or better results. This study in particular highlights a hospital-wide initiative that further confirms that standardized order sets and operating procedures for severe sepsis and septic shock result in a significant reduction in morbidity, mortality and healthcare resource consumption. With these robust findings, future emphasis should be placed on overcoming logistical, institutional and professional barriers to the implementation of standardized order sets, which can save the life of one out of every five to six patients presenting with severe sepsis and septic shock.

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### **Endocrinology & Metabolism**

Danescu, L. G., S. Levy and J. Levy (2010). "MARKEDLY LOW HEMOGLOBIN A(1c) IN A PATIENT WITH AN UNUSUAL PRESENTATION OF beta-THALASSEMIA MINOR." Endocrine Practice **16**(1): 89-92. [PDF Full-Text](#)

[Levy, Joseph] Wayne State Univ, Sch Med, Div Endocrinol, VA Med Ctr, Detroit, MI 48321 USA. [Levy, Shiri] Henry Ford Hosp, Div Endocrinol, Detroit, MI 48202 USA. [Danescu, Liviu G.] St Joseph Mercy Oakland Hosp, Dept Internal Med, Pontiac, MI USA.

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Objective: To describe very low hemoglobin A(1c) levels in a patient with type 2 diabetes mellitus and an unusual presentation of beta-thalassemia minor Methods: We present the clinical and laboratory findings of the study patient Results: A 64-year-old African American man with type 2 diabetes mellitus was referred to the endocrinology level of: 16% despite elevated clinic with I hemoglobin A(1c) blood glucose concentrations. A red blood cell survival study with chromium-51 revealed that he had, I reduced erythrocyte life span less than 25% of normal He also had a markedly elevated reticulocyte count ranging from 236 to 534 x 10(3)/mu L (reference range. 25-75 x 10(3)/mu L) The laboratory findings. which me not characteristic of beta-thalassemia minor. could be the cause of the markedly low hemoglobin A(1c) in this patient. Conclusions: Although rare, when associated with marked erythrocyte turnover. beta-thalassemia minor can lead 10 a severe reduction in HbA(1c) levels In this Scenario glycemic control is best assessed by measuring fructosamine (Endocr Pract. 2010,16:89-92)

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### **Endocrinology & Metabolism**

Peyrot, M., R. R. Rubin, D. F. Kruger and L. B. Travis (2010). "Correlates of Insulin Injection Omission." Diabetes Care **33**(2): 240-245. [PDF Full-Text](#)

[Peyrot, Mark] Loyola Univ Maryland, Dept Sociol, Baltimore, MD USA. [Peyrot, Mark; Rubin, Richard R.] Johns Hopkins Univ, Dept Med, Baltimore, MD USA. [Rubin, Richard R.] Johns Hopkins Univ, Dept Pediat, Baltimore, MD 21218 USA. [Kruger, Davida F.] Henry Ford Hlth Syst, Div Endocrinol Diabet Bone & Mineral Disorders, Detroit, MI USA. [Travis, Luther B.] Univ Texas Med Branch, Dept Pediat, Galveston, TX USA. Peyrot, M, Loyola Univ Maryland, Dept Sociol, Baltimore, MD USA. [mpeyrot@loyola.edu](mailto:mpeyrot@loyola.edu)

OBJECTIVE - The purpose Of this study Was to assess factors associated with patient frequency of intentionally skipping insulin injections. RESEARCH DESIGN AND METHODS - Data were obtained through an Internet survey of 502 U.S. adults self-identified as taking insulin by injection to treat type 1 or type 2 diabetes. Multiple regression analysis assessed independent associations of various demographic, disease, and injection-specific factors with insulin omission. RESULTS - intentional insulin omission was reported by more than half of respondents; regular omission was reported by 20%. Significant independent risk factors for insulin omission were younger age, lower income and higher education, type 2 diabetes, not. following a healthy diet, taking more daily injections, interference of injections with daily activities, and injection pain and embarrassment. Risk factors differed between type 1 and type 2 diabetic patients, with diet nonadherence more prominent in type I diabetes and age, education, income, pain, and embarrassment more prominent in type 2 diabetes. CONCLUSIONS - Whereas Most Patients did not report regular intentional omission of insulin injections, a substantial number did. Our findings suggest that it is important to identify patients who intentionally Omit insulin and be aware Of the potential risk factors identified here. For patients who report injection-related problems (interference with daily activities, injection pain, and embarrassment), providers

should consider recommending strategies and tools for addressing these problems to increase adherence to prescribed insulin regimens. This could improve clinical outcomes.

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## Endocrinology & Metabolism

Qiu, S. J., D. S. Rao, S. Palnitkar and A. M. Parfitt (2010). "Dependence of Bone Yield (Volume of Bone Formed per Unit of Cement Surface Area) on Resorption Cavity Size During Osteonal Remodeling in Human Rib: Implications for Osteoblast Function and the Pathogenesis of Age-Related Bone Loss." Journal of Bone and Mineral Research **25**(2): 423-430. [PDF Full-Text](#)

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It is both a necessary and a sufficient condition for bone to be lost with age at any surface location that during remodeling the replacement of resorbed bone is incomplete. In both the ilium and the rib, the degree of such focal imbalance is smaller on the intracortical than on the endocortical or cancellous surfaces that are adjacent to bone marrow. The reason for this difference is unknown. To further examine this question, we measured various geometric variables in 1263 osteons in rib cross sections from 65 persons, including both sexes and age ranges 20 to 30 years and 60 to 70 years (four groups). Haversian canal (HC) area did not differ significantly between sexes or age groups. Percent osteonal refilling was close to 95% in all groups and did not differ between sexes but fell slightly with age. There was a very highly significant linear relationship between osteon bone area and (osteon area + HC area) in all groups, with coefficients of determination ( $r^2$ ) greater than 0.98. The regression slopes declined slightly with age in women but not in men. There was a very highly significant quadratic relationship between osteon bone area and osteon perimeter in all groups, with  $r^2$  values greater than 0.97. The ratio osteon bone area:osteon perimeter, an index of bone yield-the volume of bone deposited on each unit area of cement surface-was strongly related to osteon area and did not differ between sexes but was slightly less in the older groups. We conclude the following: (1) The high efficiency of intracortical remodeling in the rib is confirmed, with only trivial effects of age. (2) For HC area to be maintained within narrow limits and bone balance preserved, either initial osteoblast density or osteoblast capacity (the two determinants of bone yield) or, most likely, both must increase progressively with the size of the resorption cavity, suggesting that osteoblast recruitment (relative to available surface) and osteoblast lifespan increase with the volume of bone resorbed. (3) Intracortical remodeling in the rib is more efficient than marrow-adjacent remodeling at any site, possibly because of the different relationships to the circulation. In osteonal remodeling, all molecules released from resorbed bone must travel past the sites of osteoblast recruitment and operation, but in hemiosteonal remodeling, some molecules may not be subject to this constraint. (4) If marrow-adjacent remodeling became as efficient as rib intracortical remodeling, age-related bone loss would cease to be an important medical problem. (C) 2010 American Society for Bone and Mineral Research.

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## Endocrinology & Metabolism

Scheiner, G., R. J. Sobel, D. E. Smith, A. J. Pick, D. Kruger, J. King and K. Green (2009). "Insulin Pump Therapy Guidelines for Successful Outcomes." Diabetes Educator **35**: 29S-41S. [PDF Full-Text](#)

[Scheiner, Gary] Integrated Diabet Serv, Wynnewood, PA USA. [Sobel, Robert J.; Pick, Anthony J.] Northwestern Univ, Feinberg Sch Med, Chicago, IL 60611 USA. [Smith, Daphne E.; King, Jacqueline] Univ Illinois, Chicago, IL USA. [Kruger, Davida] Henry Ford Hlth Syst, Detroit, MI USA. [Green, Karen] Dupage Med Grp, Geneva, IL USA. Scheiner, G, 300 E Lancaster Ave,Suite 111, Wynnewood, PA 19096 USA. [garyscheiner@prodigy.net](mailto:garyscheiner@prodigy.net)

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## Eye Care Services

Barnett, E. M., A. Fantin, B. S. Wilson, M. A. Kass and M. O. Gordon (2010). "The Incidence of Retinal Vein Occlusion in the Ocular Hypertension Treatment Study." Ophthalmology **117**(3): 484-488. [PDF Full-Text](#)

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**Objective:** To determine the incidence of retinal vein occlusion (RVO) in the Ocular Hypertension Treatment Study (OHTS). **Design:** Retrospective analysis of data from a randomized clinical trial. **Participants:** We included 1636 ocular hypertensive participants with a mean follow-up of 9.1 years. Participants in the medication and observation groups were managed according to their original randomization assignment until June 1, 2002. At that time, the observation participants were offered ocular hypotensive treatment. Data to July 1, 2005, are included in this report. **Methods:** Occurrences of RVO in study participants, categorized as branch, central or hemicentral vein occlusion, were documented. Potential RVO events were identified by a keyword search of Adverse Event Reports, the Optic Disc Reading Center database, Endpoint Committee reviews, and by response to a written request for information sent to each clinical site. To confirm a potential RVO, the complete OHTS chart was reviewed. **Statistical analyses** included t tests, chi-square tests and Cox proportional hazards models. **Main Outcome Measures:** Incidence of RVO. **Results:** Twenty-six RVOs-5 branch, 14 central, and 7 hemicentral RVOs-were confirmed in 23 participants (15 observation and 8 medication). The 10-year cumulative incidence of RVO was 2.1% in the observation group and 1.4% in the medication group (P = 0.14; log-rank test). At baseline, participants who later developed a RVO were significantly older (65.1 vs 55.3 years; P = 0.01), and had greater horizontal cup-to-disc ratios (P = 0.0004). **Conclusions:** Although the incidence of RVO was higher in the observation group than the medication group, this difference did not attain significance. Consistent with some previous studies, older age and greater cup-to-disc ratio were associated with the development of RVO. **Financial Disclosure(s):** Proprietary or commercial disclosure may be found after the references. *Ophthalmology* 2010; 117: 484-488 (C) 2010 by the American Academy of Ophthalmology.

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## Eye Care Services

Demirci, H., B. R. Frueh and C. C. Nelson (2010). "Marcus Gunn Jaw-Winking Synkinesis Clinical Features and Management." Ophthalmology **EPub Ahead of Print**. [PDF Full-Text](#)

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**OBJECTIVE:** To evaluate the clinical features including eyelid excursion and management of Marcus Gunn jaw-winking synkinesis (MGJWS). **DESIGN:** Observational case series. **PARTICIPANTS:** Forty-eight consecutive patients with MGJWS. **METHODS:** Clinical features and management of 48 patients with MGJWS were reviewed retrospectively. Upper eyelid excursion was measured and graded. Complications of surgical intervention were evaluated. **MAIN OUTCOME MEASURES:** Resolution of MGJWS and symmetry of upper eyelids in primary position. **RESULTS:** Excursion of the ptotic eyelid with jaw movement in MGJWS was graded as mild (<2 mm) in 16% of patients, moderate (2-4 mm) in 76% of patients, and severe (>=5 mm) in 8% of patients. Thirty patients with moderate or severe MGJWS underwent disabling of the involved levator muscle and bilateral or unilateral frontalis suspension and had more than 6 months of follow-up. After a mean follow-up of 62 months, MGJWS resolved in 29 (97%) patients and improved from 6 mm to 2 mm in 1 (3%) patient. Relative upper eyelid height was within 1 mm in 87% of patients in primary position and within 1 mm in 80% of patients in downgaze. Twenty-six patients had bilateral frontalis suspension with disabling of unilateral levator muscle on the involved side. Relative upper eyelid height was within 1 mm in 88% of patients in the primary position and within 1 mm in 88% of patients in downgaze. Four non-amblyopic patients had unilateral frontalis suspension with levator muscle disabling. Relative upper eyelid height was symmetrical in 75% of the patients in primary position and in 25% of patients in downgaze. Complications included eyelash ptosis in 10% of the patients, loss of eyelid crease in 10%, and entropion in 3%. **CONCLUSIONS:** Most of the patients with MGJWS exhibited moderate eyelid excursion. Disabling of the involved levator muscle and bilateral frontalis suspension and, in selected cases, disabling of the involved levator muscle and unilateral frontalis suspension were effective in the treatment of MGJWS. Eyelash ptosis and loss of eyelid crease were the most common complications, each occurring in 10% of the patients. **FINANCIAL DISCLOSURE(S):** The author(s) have no proprietary or commercial interest in any materials discussed in this article.

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## Gastroenterology

Gordon, S. C., D. Moonka, K. A. Brown, C. Rogers, M. A. Huang, N. Bhatt and L. Lamerato (2010). "Risk for Renal Cell Carcinoma in Chronic Hepatitis C Infection." Cancer Epidemiol Biomarkers Prev **Epub Ahead of Print**. [Article Request Form](#)

Authors' Affiliations: Division of Gastroenterology and Hepatology, and Departments of Urology and Biostatistics and Research Epidemiology, Henry Ford Hospital; and Wayne State University School of Medicine, Detroit, Michigan.

**BACKGROUND:** Chronic infection with hepatitis C virus (HCV) confers increased risk for chronic renal disease, and numerous reports suggest an association with renal cell carcinoma (RCC), a cancer with rapidly rising global incidence. We sought to determine whether HCV infection confers an increased risk for developing RCC. **METHODS:** With the use of administrative data from a large, integrated, and ethnically diverse healthcare system, we did a cohort study of 67,063 HCV-tested patients between 1997 and 2006 who were followed for the development of RCC until April 2008. **RESULTS:** A search of the health system cancer registry for patients with the diagnosis of kidney cancer showed that RCC was diagnosed in 0.6% (17 of 3,057) of HCV-positive patients versus 0.3% (177 of 64,006) of HCV-negative patients. The mean age at RCC diagnosis was much younger in HCV-positive individuals (54 versus 63;  $P < 0.001$ ). The univariate hazard ratio for RCC among HCV patients was 2.20 (95% confidence interval, 1.32-3.67;  $P = 0.0025$ ). In a multivariate model that included the risk factors age, African-American race, male gender, and chronic kidney disease, the overall hazard ratio for RCC among HCV patients was 1.77 (95% confidence interval, 1.05-2.98;  $P = 0.0313$ ). **CONCLUSION:** Chronic HCV infection confers a risk for the development of RCC. Impact: Clinicians should consider newly identified renal lesions in patients with chronic HCV infection with a heightened suspicion for neoplasm, and newly diagnosed cases of RCC may require more careful surveillance for the presence of HCV infection. Additional studies are required to confirm these findings and to explore potential mechanisms of oncogenesis. *Cancer Epidemiol Biomarkers Prev*; 19(4); OF1-8.

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## Hypertension & Vascular Research

Herrera, M. and J. L. Garvin (2010). "Angiotensin II stimulates thick ascending limb NO production via AT<sub>2</sub> receptors and Akt1-dependent nitric oxide synthase 3 (NOS3) activation." J Biol Chem **Epub Ahead of Print**. [PDF Full-Text](#)

Henry Ford Hospital, United States.

Angiotensin-II (Ang II) acutely stimulates thick ascending limbs (TALs) NO via an unknown mechanism. In endothelial cells, activation of AT<sub>2</sub> stimulates NO. Akt1 activates NOS3 by direct phosphorylation. We hypothesized that Ang II stimulates TAL NO production via AT<sub>2</sub>-mediated Akt1 activation, which phosphorylates NOS3 at serine-1177. We measured NO production by fluorescence microscopy. In isolated TALs, Ang II (100nM) increased NO production by 10.3±2.3 fluorescence units/min (f.u./min)( $p < 0.01$ ). Ang II increased cGMP accumulation by 4.9±1.3 fmol/mug ( $p < 0.01$ ). On adding the AT<sub>2</sub> antagonist PD123319 (1μM), Ang II failed to stimulate NO (0.9±2.7 f.u./min;  $p < 0.001$  vs. Ang II); adding the AT<sub>1</sub> antagonist losartan (1μM) resulted in Ang II stimulating NO by 8.9±0.7 f.u./min. Akt inhibitor (5μM) blocked Ang II-stimulated NO (-0.1±0.2 f.u./min vs. inhibitor alone). PhosphoAkt1 increased by 72% after 5 min ( $p < 0.006$ ), returning to basal after 10 min. PhosphoAkt2 did not change after 5 min but increased by 115 and 163% after 10 and 15 min ( $p < 0.02$ ). PhosphoAkt3 did not change. An AT<sub>2</sub> agonist increased pAkt1 by 78% ( $p < 0.02$ ), PI3-kinase inhibition blocked this effect. In TALs transduced with dominant negative Akt1, Ang II failed to stimulate NO (1.0±1.9 f.u./min vs. 11.7±1.6 for controls;  $p < 0.001$ ). Ang II increased phosphoNOS3 at serine-1177 by 130% ( $p < 0.01$ ) and 150% after 5 and 10 min ( $p < 0.02$ ). Ang II increased phosphoNOS3 at serine-633 by 50% after 5 min ( $p < 0.01$ ). Akt inhibition prevented NOS3 phosphorylation. We concluded that Ang II enhances TAL NO production via activation of AT<sub>2</sub> and Akt1-dependent phosphorylation of NOS3 at serines 1177 and 633.

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## Hypertension & Vascular Research

Liao, T. D., X. P. Yang, M. D'Ambrosio, Y. Zhang, N. E. Rhaleb and O. A. Carretero (2010). "N-acetyl-seryl-aspartyl-lysyl-proline attenuates renal injury and dysfunction in hypertensive rats with reduced renal mass: council for high blood pressure research." Hypertension **55**(2): 459-67. 2809792. [PDF Full-Text](#)

Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Hospital, Detroit, Mich 48202-2689, USA.

N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a naturally occurring peptide of which the plasma concentration is increased 4- to 5-fold by angiotensin-converting enzyme inhibitors. We reported previously that, in models of both hypertension and postmyocardial infarction, Ac-SDKP reduces cardiac inflammation and fibrosis. However, it is unknown whether Ac-SDKP can prevent or reverse renal injury and dysfunction in hypertension. In the present study, we tested the hypothesis that, in rats with 5/6 nephrectomy (5/6Nx)-induced hypertension, Ac-SDKP reduces renal damage, albuminuria, and dysfunction by decreasing inflammatory cell infiltration and renal fibrosis and by increasing nephrin protein. Ac-SDKP (800 microg/kg per day, SC via osmotic minipump) or vehicle was either started 7 days before 5/6Nx (prevention) and continued for 3 weeks or started 3 weeks after 5/6Nx (reversal) and continued for another 3 weeks. Rats with 5/6Nx developed high blood pressure, left ventricular hypertrophy, albuminuria, decreased glomerular filtration rate, and increased macrophage infiltration (inflammation) and renal collagen content (fibrosis). Ac-SDKP did not affect blood pressure or left ventricular hypertrophy in either group; however, it significantly reduced albuminuria, renal inflammation, and fibrosis and improved glomerular filtration rate in both prevention and reversal groups. Moreover, slit diaphragm nephrin protein expression in the glomerular filtration barrier was significantly decreased in hypertensive rats. This effect was partially prevented or reversed by Ac-SDKP. We concluded that Ac-SDKP greatly attenuates albuminuria and renal fibrosis and improves renal function in rats with 5/6Nx. These effects may be related to decreased inflammation (macrophages) and increased nephrin protein.

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### **Hypertension & Vascular Research**

Silva, G. B. and J. L. Garvin (2010). "Rac1 mediates NaCl-induced superoxide generation in the thick ascending limb." Am J Physiol Renal Physiol **298**(2): F421-5. 2822510. [PDF Full-Text](#)

Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan 48202, USA.

Superoxide (O<sub>2</sub><sup>-</sup>) produced by NADPH oxidase regulates Na absorption and renal hemodynamics. Increased NaCl in the thick ascending limb (TAL) stimulates O<sub>2</sub><sup>-</sup> generation. However, we do not know whether physiological changes in NaCl concentration augment O<sub>2</sub><sup>-</sup> generation, nor do we know the mediator(s) involved. In other cells, Rac1, a regulatory subunit of NADPH oxidase, is activated by elevated NaCl. We hypothesized that increasing luminal NaCl within the physiological range activates Rac1 and NADPH oxidase and, thereby, increases O<sub>2</sub><sup>-</sup> production. We increased NaCl from 10 to 57 mM in medullary TAL suspensions and used lucigenin to measure O<sub>2</sub><sup>-</sup> generation and Western blot to measure Rac1 activity. Increasing NaCl stimulated O<sub>2</sub><sup>-</sup> generation from 1.41 ± 0.16 to 2.71 ± 0.30 nmol O<sub>2</sub><sup>-</sup> x min<sup>-1</sup> x mg protein<sup>-1</sup> (n = 6, P < 0.05). This increase was blocked by the Na-K-2Cl cotransporter inhibitor furosemide and the NADPH oxidase inhibitor apocynin. To examine the role of Rac1 in NaCl-induced O<sub>2</sub><sup>-</sup> production, we measured Rac1 translocation by Western blot. When we added NaCl, Rac1 in the particulate fraction increased from 6.8 ± 0.8 to 11.7 ± 2.4% of total Rac1 (n = 7, P < 0.05). Then we measured O<sub>2</sub><sup>-</sup> generation in the presence and absence of the Rac1 inhibitor. In the absence of the Rac1 inhibitor, NaCl increased O<sub>2</sub><sup>-</sup> generation from 1.07 ± 0.24 to 2.02 ± 0.49 nmol O<sub>2</sub><sup>-</sup> x min<sup>-1</sup> x mg protein<sup>-1</sup>, and this increase was completely blocked by the inhibitor. Similarly, in vivo treatment of TALs with adenovirus expressing dominant-negative Rac1 decreased NaCl-induced O<sub>2</sub><sup>-</sup> generation by 60% compared with control (0.33 ± 0.04 vs. 0.81 ± 0.17 nmol O<sub>2</sub><sup>-</sup> x min<sup>-1</sup> x mg protein<sup>-1</sup>), n = 6, P < 0.05). We concluded that physiological increases in NaCl stimulate TAL O<sub>2</sub><sup>-</sup> generation by activating Rac1.

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### **Hypertension & Vascular Research**

Wang, F., Q. He, Y. Sun, X. Dai and X. P. Yang (2010). "Female Adult Mouse Cardiomyocytes Are Protected Against Oxidative Stress." Hypertension **EPub Ahead of Print**. [PDF Full-Text](#)

Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Hospital, Detroit, Mich; Department of Pathology, North China Coal Medical College, Tangshan, China.

Premenopausal women have less cardiovascular disease and lower cardiovascular morbidity and mortality than men the same age. Our previous studies showed that female mice have lower mortality and better preserved cardiac function after myocardial infarction. However, the precise cellular and molecular mechanisms responsible for such a sex difference are not well established. Using cultured adult mouse cardiomyocytes, we tested the hypothesis that the survival advantage of females stems from activated estrogen receptors and Akt survival signaling pathways. Adult mouse cardiomyocytes were isolated from male and female C57BL/6J mice and treated with hydrogen peroxide (100  $\mu\text{mol/L}$ ) for 30 minutes. Cell survival was indicated by rod ratio (rod shaped cells:total cells), cell death by lactate dehydrogenase release, and positive staining of annexin-V (a marker for apoptosis) and propidium iodide (a marker for necrosis). In response to hydrogen peroxide, female adult mouse cardiomyocytes exhibited a higher rod ratio, lower lactate dehydrogenase release, and fewer Annexin-V-positive and propidium iodide-positive cells compared with males. Phospho-Akt was greater in females both at baseline and after hydrogen peroxide stimulation. The downstream molecule of Akt, phospho-GSK-3 $\beta$  (inactivation), was also higher, whereas caspase 3 activity was lower in females in response to hydrogen peroxide. Bcl-2 did not differ between sexes. Estrogen receptor- $\alpha$  was the dominant isoform in females, whereas estrogen receptor- $\beta$  was low but similar in both sexes. Our findings demonstrate that female adult mouse cardiomyocytes have a greater survival advantage when challenged with oxidative stress-induced cell death. This may be attributable to activation of Akt and inhibition of GSK-3 $\beta$  and caspase 3 through an estrogen receptor- $\alpha$ -mediated mechanism.

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### **Infectious Diseases**

Moore, C. L., P. Osaki-Kiyan, M. Perri, S. Donabedian, N. Z. Haque, A. Chen and M. J. Zervos (2010). "USA600 (ST45) Methicillin-Resistant Staphylococcus aureus Bloodstream Infections in Urban Detroit." J Clin Microbiol **Epub Ahead of Print**. [PDF Full-Text](#)

Henry Ford Hospital, Detroit, MI; Wayne State University Medical School, Detroit, MI.

Methicillin-resistant Staphylococcus aureus (MRSA) has emerged as a major source of invasive infections, implicated in 18,000 deaths annually (9)....

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### **Infectious Diseases**

Reyes, K., R. Malik, C. Moore, S. Donabedian, M. Perri, L. Johnson and M. Zervos (2010). "Evaluation of risk factors for coinfection or cocolonization with vancomycin-resistant enterococcus and methicillin-resistant Staphylococcus aureus." J Clin Microbiol **48(2)**: 628-30. 2815608. [PDF Full-Text](#)

Division of Infectious Diseases, Henry Ford Health System, Detroit, MI 48202, USA.

We retrospectively evaluated 410 patients with coinfection or cocolonization due to vancomycin-resistant (VR) enterococcus (VRE) and methicillin-resistant Staphylococcus aureus (MRSA). The prevalence rate was 19.8%. Risk factors included isolation of VR Enterococcus faecalis and use of linezolid or clindamycin. Inc18-like vanA plasmids were found in 7% of VR E. faecalis isolates and none of the VR E. faecium isolates.

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### **Internal Medicine**

Arango, B. A., A. B. Castellon, C. A. Perez, L. E. Ruez and E. S. Santos (2010). "Nasopharyngeal carcinoma: alternative treatment options after disease progression." Expert Rev Anticancer Ther **10(3)**: 377-86. [Article Request Form](#)

Department of Internal Medicine, Henry Ford Hospital, 2799 W Grand Blvd., Detroit, MI 48202-2689, USA.  
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Nasopharyngeal carcinoma is a rare malignancy with an incidence well under one per 100,000 person-years, except for some geographic areas, such as Asia. The prognosis of nasopharyngeal carcinoma is related to its potential for locoregional invasion and metastatic spread. Radiotherapy alone remains the standard treatment for early stages. However, for locally advanced disease, chemotherapy may offer some benefit as a radiosensitizer while treating microscopic spread disease. Chemoradiotherapy is now the standard treatment for locally advanced and/or node-positive patients. Platinum-based therapy is the preferred regimen for this therapeutic approach. In this review, we discuss all treatment modalities available for nasopharyngeal carcinoma, including the standard of care and what therapeutic options could be available for those patients who progress after the standard treatment has been delivered.

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### **Internal Medicine**

Novak, J. E. and L. A. Szczech (2010). "Management of HIV-infected patients with ESRD." Adv Chronic Kidney Dis **17**(1): 102-10. [PDF Full-Text](#)

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Patients infected with human immunodeficiency virus (HIV) often progress to ESRD. In the era of highly active antiretroviral therapy, the care of these patients has become increasingly complex as survival has improved. Patients infected with HIV who also have ESRD are at risk for critical interactions between medication regimens to treat both of these conditions. Within this population, hemo- and peritoneal dialysis as well as kidney transplantation are life sustaining but present a host of obstacles related to HIV monitoring and risk of transmission, access thrombosis, infection, and rejection. Knowledge of antiretroviral regimens, drug interactions, and HIV resistance as well as the management of ESRD in the presence of HIV infection will improve the care of these unique patients.

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### **Internal Medicine**

Sequeira-Lopez, M. L. S., E. T. Weatherford, G. R. Borges, M. C. Monteagudo, E. S. Pentz, B. D. Harfe, O. Carretero, C. D. Sigmund and R. A. Gomez (2010). "The MicroRNA-Processing Enzyme Dicer Maintains Juxtaglomerular Cells." Journal of the American Society of Nephrology **21**(3): 460-467. [PDF Full-Text](#)

[Sequeira-Lopez, Maria Luisa S.; Monteagudo, Maria C.; Pentz, Ellen S.; Gomez, R. Ariel] Univ Virginia, Sch Med, Dept Pediat, Charlottesville, VA 22908 USA. [Weatherford, Eric T.; Borges, Julianna R.; Sigmund, Curt D.] Univ Iowa, Dept Internal Med, Iowa City, IA 52242 USA. [Weatherford, Eric T.; Borges, Julianna R.; Sigmund, Curt D.] Univ Iowa, Dept Mol Physiol & Biophys, Iowa City, IA 52242 USA. [Harfe, Brian D.] Univ Florida, Coll Med, Dept Mol Genet & Microbiol, Gainesville, FL USA. [Carretero, Oscar] Henry Ford Hosp, Dept Internal Med, Detroit, MI 48202 USA.

Sequeira-Lopez, MLS, Univ Virginia, Sch Med, Dept Pediat, 409 Lane Rd, MR4 Bldg Room 2001, Charlottesville, VA 22908 USA. [mssl7u@virginia.edu](mailto:mssl7u@virginia.edu) [rg@virginia.edu](mailto:rg@virginia.edu)

Juxtaglomerular cells are highly specialized myoepithelioid granulated cells located in the glomerular afferent arterioles. These cells synthesize and release renin, which distinguishes them from other cells. How these cells maintain their identity, restricted localization, and fate is unknown and is fundamental to the control of BP and homeostasis of fluid and electrolytes. Because microRNAs may control cell fate via temporal and spatial gene regulation, we generated mice with a conditional deletion of Dicer, the RNase III endonuclease that produces mature microRNAs in cells of the renin lineage. Deletion of Dicer severely reduced the number of juxtaglomerular cells, decreased expression of the renin genes (Ren1 and Ren2), lowered plasma renin concentration, and decreased BP. As a consequence of the disappearance of renin-producing cells, the kidneys developed striking vascular abnormalities and prominent striped fibrosis. We conclude that microRNAs maintain the renin-producing juxtaglomerular cells and the morphologic integrity and function of the kidney.

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### **Internal Medicine**

Simon, M. R., M. Jan, J. Yee, U. S. Nori, J. Hu, C. Akin and L. B. Schwartz (2010). "Tryptase Is Not Cleared by the Kidneys into the Urine." International Archives of Allergy and Immunology **152**(1): 28-31. [Article Request Form](#)

[Simon, Michael R.] William Beaumont Hosp, Allergy & Immunol Sect, Royal Oak, MI 48073 USA. [Simon, Michael R.] Wayne State Univ, Sch Med, Dept Internal Med, Detroit, MI 48201 USA. [Simon, Michael R.] Wayne State Univ, Sch Med, Dept Pediat, Detroit, MI 48201 USA. [Jan, Mindy; Yee, Jerry; Nori, Uday S.] Henry Ford Hosp, Dept Med, Dept Hypertens & Nephrol, Detroit, MI 48202 USA. [Hu, Jiang; Schwartz, Lawrence B.] Virginia Commonwealth Univ, Dept Med, Div Rheumatol Allergy & Immunol, Richmond, VA 23298 USA. [Hu, Jiang] Univ Michigan, Div Clin Immunol & Allergy, Ann Arbor, MI 48109 USA. Simon, MR, William Beaumont Hosp, Allergy & Immunol Sect, Royal Oak, MI 48073 USA.  
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Background: Patients with chronic kidney disease have been reported to have increased concentrations of blood tryptase. Detection of tryptase in the urine of healthy subjects has been reported. Objective: The objective is to determine whether tryptase is indeed cleared by the kidneys. Methods: Blood and urine collections were performed in healthy and systemic mastocytosis subjects. Total and mature tryptase concentrations in blood and total tryptase concentrations in urine were determined. Results: Total tryptase levels in urine were below the limit of detection in both healthy subjects and those with systemic mastocytosis, even after concentrating the urine 10-fold. Thus, both mature and protryptase levels in urine are <0.2 ng/ml. Conclusion: Tryptase is not cleared by the kidneys into the urine. Copyright (C) 2009 S. Karger AG, Basel

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### Internal Medicine

Tucciarone, M., P. A. Dileo, E. R. Castro and M. Guerrero (2009). "Myocardial infarction secondary to carbon monoxide poisoning: an uncommon presentation of a common condition. Case report and review of the literature." Am J Ther **16**(5): 462-5. [PDF Full-Text](#)

Department of Medicine, Henry Ford Hospital, Detroit, MI 48202, USA.

Acute carbon monoxide poisoning is the most common cause of death from poisoning in the United States. It causes a spectrum of myocardial injury irrespective of carboxyhemoglobin levels and coronary anatomy. We present a 34-year-old woman with a non-ST-segment elevation myocardial infarction secondary to carbon monoxide poisoning who had normal coronary arteries by coronary angiography. A review of the literature is discussed.

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### Medical Genetics

Micale, M., J. Insko, S. A. D. Ebrahim, A. Adeyinka, C. Runke and D. L. Van Dyke (2010). "Double trisomy revisited-a multicenter experience." Prenatal Diagnosis **30**(2): 173-176. [PDF Full-Text](#)

[Micale, Mark; Insko, Janet] William Beaumont Hosp, Dept Anat Pathol, Royal Oak, MI 48073 USA. [Micale, Mark] Oakland Univ, William Beaumont Sch Med, Rochester, MI 48063 USA. [Ebrahim, Salah A. D.] Wayne State Univ, Sch Med, Detroit, MI USA. [Ebrahim, Salah A. D.] DMC Univ Labs, Detroit, MI USA. [Adeyinka, Adewale] Henry Ford Hosp, Dept Med Genet, Detroit, MI 48202 USA. [Runke, Cassandra; Van Dyke, Daniel L.] Mayo Clin, Dept Pathol & Lab Med, Rochester, MN USA. Micale, M, William Beaumont Hosp, Dept Anat Pathol, 3601 W Thirteen Mile Rd, Royal Oak, MI 48073 USA.  
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### Nephrology

Yee, J. (2010). "Iron replacement therapy: assessing today's options to prepare for bundling." Nephrol News Issues **24**(2): suppl 1-8. [Article Request Form](#)

Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan, USA.

New Medicare rules that set forth a revised reimbursement scheme for dialysis services will introduce significant changes for providers. The new rules will abandon the current system of separate reimbursement for drugs associated with the hemodialysis services, including erythropoiesis-stimulating agents (ESAs) and intravenous (i.v.) iron. These rules will "bundle" these agents and related laboratory tests into a single, case-

mix adjusted composite rate. These bundling rules will be gradually phased-in, beginning in 2011. One of the primary effects of the new reimbursement policy will be to discourage over-utilization of ESAs that comprise nearly one-quarter of hemodialysis-related Medicare expenditures. As a result, hemodialysis providers will be challenged to make hemodialysis services more cost-effective, while ensuring that Medicare clinical performance measures are met and patient care is not compromised. i.v. iron has an integral role in making anemia care more cost-effective in the hemodialysis setting by improving measures of iron-deficiency anemia, maintaining necessary iron balance, and reducing the utilization of ESAs. This review discusses the potential benefits of i.v. iron in the management of hemodialysis patients with iron-deficiency anemia. It also focuses on the available i.v. iron options, particularly the established efficacy and safety profile of i.v. iron dextran compared with other i.v. iron formulations as well as cost considerations.

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## Neurology

Jiang, Q., Z. G. Zhang and M. Chopp (2010). "MRI of stroke recovery." *Stroke* **41**(2): 410-4.

[PDF Full-Text](#)

Department of Neurology, Henry Ford Hospital System, NMR Laboratory, Detroit, Mich 48202, USA.

[qjiang1@hfhs.org](mailto:qjiang1@hfhs.org)

MRI is a vital tool for the measurement of acute stroke and has been used to visualize changes in activation patterns during stroke recovery. There is emerging interest on using MRI to monitor the structural substrates of spontaneous recovery and neurorestorative treatment of stroke. In this review, we describe the use of MRI and its associated challenges to measure vascular and neuronal remodeling in response to spontaneous and therapy-induced stroke recovery. We demonstrate that MRI methodologies may be used in real-time monitoring of recovery from stroke.

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## Neurology

Lewitt, P. A. (2010). "Relief of parkinsonism and dyskinesia. One and the same dopaminergic mechanism?" *Neurology* **Epub Ahead of Print**. [PDF Full-Text](#)

From the Departments of Neurology, Henry Ford Hospital and Wayne State University School of Medicine, Detroit, MI.

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## Neurology

Li, L., Q. Jiang, G. L. Ding, L. Zhang, Z. G. Zhang, Q. J. Li, S. Panda, M. Lu, J. R. Ewing and M. Chopp (2010). "Effects of administration route on migration and distribution of neural progenitor cells transplanted into rats with focal cerebral ischemia, an MRI study." *Journal of Cerebral Blood Flow and Metabolism* **30**(3): 653-662. [PDF Full-Text](#)

[Li, Lian; Jiang, Quan; Ding, Guangliang; Zhang, Li; Zhang, Zheng Gang; Li, Qingjiang; Panda, Swayamprava; Ewing, James R.; Chopp, Michael] Henry Ford Hosp, Dept Neurol, Detroit, MI 48202 USA. [Lu, Mei] Henry Ford Hosp, Dept Biostat & Res Epidemiol, Detroit, MI 48202 USA. [Chopp, Michael] Oakland Univ, Dept Phys, Rochester, MI USA.

Jiang, Q, Henry Ford Hosp, Dept Neurol, B126, Educ & Res Bldg, 2799 W Grand Blvd, Detroit, MI 48202 USA.

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We tested the hypotheses that administration routes affect the migration and distribution of grafted neural progenitor cells (NPCs) in the ischemic brain and that the ischemic lesion plays a role in mediating the grafting process. Male Wistar rats (n = 41) were subjected to 2-h middle cerebral artery occlusion (MCAo), followed 1 day later by administration of magnetically labeled NPCs. Rats with MCAo were assigned to one of three treatment groups targeted for cell transplantation intra-arterially (IA), intracisternally (IC), or intravenously (IV). MRI measurements consisting of T2-weighted imaging and three-dimensional (3D) gradient echo imaging were performed 24 h after MCAo, 4 h after cell injection, and once a day for 4 days. Prussian blue staining was used to identify the labeled cells, 3D MRI to detect cell migration and distribution, and T2 map to assess lesion volumes. Intra-arterial (IA) administration showed significantly increased migration, a far more diffuse distribution pattern, and a larger number of transplanted NPCs in the target brain than IC or IV administration.

However, high mortality with IA delivery (IA: 41%; IC: 17%; IV: 8%) poses a serious concern for using this route of administration. Animals with smaller lesions at the time of transplantation have fewer grafted cells in the parenchyma. *Journal of Cerebral Blood Flow & Metabolism* (2010) 30, 653-662; doi: 10.1038/jcbfm.2009.238; published online 4 November 2009

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## Neurology

Mikkelsen, T., N. A. Paleologos, P. D. Robinson, M. Ammirati, D. W. Andrews, A. L. Asher, S. H. Burri, C. S. Cobbs, L. E. Gaspar, D. Kondziolka, M. E. Linskey, J. S. Loeffler, M. McDermott, M. P. Mehta, J. J. Olson, R. A. Patchell, T. C. Ryken and S. N. Kalkanis (2010). "The role of prophylactic anticonvulsants in the management of brain metastases: a systematic review and evidence-based clinical practice guideline." *J Neurooncol* **96**(1): 97-102. 2808526. [PDF Full-Text](#)

Department of Neurology, Henry Ford Health System, Detroit, MI, USA.

QUESTION : Do prophylactic anticonvulsants decrease the risk of seizure in patients with metastatic brain tumors compared with no treatment? TARGET POPULATION: These recommendations apply to adults with solid brain metastases who have not experienced a seizure due to their metastatic brain disease.

RECOMMENDATION: Level 3 For adults with brain metastases who have not experienced a seizure due to their metastatic brain disease, routine prophylactic use of anticonvulsants is not recommended. Only a single underpowered randomized controlled trial (RCT), which did not detect a difference in seizure occurrence, provides evidence for decision-making purposes.

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## Neurology

Xiong, Y., A. Mahmood and M. Chopp (2010). "Angiogenesis, neurogenesis and brain recovery of function following injury." *Curr Opin Investig Drugs* **11**(3): 298-308. 2836170. [Article Request Form](#)

Henry Ford Health System, Department of Neurology, E&R Building, 2799 West Grand Boulevard, Detroit, MI 48202, USA.

Stroke and traumatic brain injury (TBI) are major causes of mortality and morbidity worldwide. Unfortunately, almost all phase III clinical trials of neuroprotective agents for stroke and TBI have demonstrated no benefit, raising concerns regarding the use of neuroprotective strategies alone as therapy for acute brain injuries. Therefore, a compelling need exists to develop treatments that promote both the repair and regeneration of injured brain tissue, and functional recovery. Recent data suggest that strategies to enhance neurogenesis and angiogenesis following brain injuries may provide promising opportunities to improve clinical outcomes and brain functional recovery. This review discusses neurogenesis and angiogenesis in the adult brain following stroke or TBI. Selected cell-based and pharmacological therapies are highlighted that promote neurogenesis and angiogenesis and are designed to restore neurological function after brain injuries. These discoveries emphasize the need for an improved understanding of injury- and therapy-induced neurogenesis and angiogenesis in the adult brain, and suggest that the manipulation of endogenous neural precursors and endothelial cells is a potential therapy for brain injury.

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## Neurology

Xu, P., M. Z. Qiu, Z. Y. Zhang, C. S. Kang, R. C. Jiang, Z. F. Jia, G. X. Wang, H. Jiang and P. Y. Pu (2010). "The oncogenic roles of Notch1 in astrocytic gliomas in vitro and in vivo." *Journal of Neuro-Oncology* **97**(1): 41-51. [PDF Full-Text](#)

[Xu, Peng; Qiu, Mingzhe; Zhang, Zhiyong; Kang, Chunsheng; Jiang, Rongcai; Jia, Zhifan; Wang, Guangxiu; Pu, Peiyu] Tianjin Med Univ, Gen Hosp, Dept Neurosurg, Tianjin 300052, Peoples R China. [Xu, Peng; Qiu, Mingzhe; Zhang, Zhiyong; Kang, Chunsheng; Jiang, Rongcai; Jia, Zhifan; Wang, Guangxiu; Pu, Peiyu] Tianjin Neurol Inst, Lab Neurooncol, Tianjin 300052, Peoples R China. [Jiang, Hao] Henry Ford Hosp, Dept Neurol, Detroit, MI 48202 USA.

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Notch receptors play an essential role in cellular processes during embryonic and postnatal development, including maintenance of stem cell self-renewal, proliferation, and determination of cell fate and apoptosis. Deregulation of Notch signaling has been implicated in some genetic diseases and tumorigenesis. The function of Notch signaling in a variety of tumors can be either oncogenic or tumor-suppressive, depending on the cellular context. In this study, Notch1 overexpression was observed in the majority of 45 astrocytic gliomas with different grades and in U251MG glioma cells. Transfection of siRNA targeting Notch1 into U251 cells in vitro downregulated Notch1 expression, associated with inhibition of cell growth, arrest of cell cycle, reduction of cell invasiveness, and induction of cell apoptosis. Meanwhile, tumor growth was delayed in established subcutaneous gliomas in nude mice treated with Notch1 siRNA in vivo. These results suggest that Notch1 plays an important oncogenic role in the development and progression of astrocytic gliomas. Furthermore, knockdown of Notch1 expression by siRNA simultaneously downregulated the expression of EGFR and the important components of its downstream pathways, including PI3K, p-AKT, K-Ras, cyclin D1 and MMP9, indicating the crosstalk and interaction of Notch and EGFR signaling pathways.

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## Neurology

Zacharek, A., A. Shehadah, J. L. Chen, X. Cui, C. Roberts, M. Lu and M. Chopp (2010). "Comparison of Bone Marrow Stromal Cells Derived From Stroke and Normal Rats for Stroke Treatment." *Stroke* **41**(3): 524-530. [PDF Full-Text](#)

[Zacharek, Alex; Shehadah, Amjad; Chen, Jieli; Cui, Xu; Roberts, Cynthia; Chopp, Michael] Henry Ford Hlth Sci Ctr, Dept Neurol, Detroit, MI USA. [Lu, Mei] Henry Ford Hlth Sci Ctr, Dept Biostat & Res Epidemiol, Detroit, MI USA. [Chopp, Michael] Oakland Univ, Dept Phys, Rochester, MI USA.  
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Background and Purpose-We compared the effect of treatment of stroke with bone marrow stromal cells from stroke rats (Isch-BMSC) and normal rats (Nor-BMSC) on functional outcome. Methods-Isch-BMSCs and Nor-BMSCs were intravenously injected into rats 24 hours after middle cerebral artery occlusion. To test the mechanism of Isch-BMSC-enhanced neurorestoration, Isch-BMSC and Nor-BMSC cultures were used. Results-Isch-BMSC significantly promoted functional outcome and enhanced angiogenesis, arterial density, and axonal regeneration compared with Nor-BMSC treatment animals. Isch-BMSCs exhibited increased Angiopoietin-1, Tie2, basic fibroblast growth factor, glial cell-derived neurotrophic factor, vascular endothelial growth factor, and Fik1 gene expression compared with Nor-BMSC. Using transwell coculture of BMSCs with brain-derived endothelial cells, Isch-BMSCs increased phosphorylated-Tie2 activity in brain-derived endothelial cells and enhanced brain-derived endothelial cells capillary tube formation compared with Nor-BMSCs. Inhibition of Tie2 gene expression in brain-derived endothelial cells using siRNA significantly attenuated BMSC-induced capillary tube formation. Conclusions-These data suggest that Isch-BMSCs are superior to Nor-BMSCs for the neurorestorative treatment of stroke, which may be mediated by the enhanced trophic factor and angiogenic characteristics of Isch-BMSCs. (*Stroke*. 2010;41:524-530.)

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## Neurology

Zhang, L., Z. G. Zhang, B. Buller, J. Jiang, Y. Jiang, D. Zhao, X. Liu, D. Morris and M. Chopp (2010). "Combination Treatment With VELCADE and Low-Dose Tissue Plasminogen Activator Provides Potent Neuroprotection in Aged Rats After Embolic Focal Ischemia." *Stroke* **Epub Ahead of Print**. [PDF Full-Text](#)

From the Departments of Neurology and Emergency Medicine, the Henry Ford Health System, Detroit, Mich; and the Department of Physics, Oakland University, Rochester, Mich.

**BACKGROUND AND PURPOSE:** Treatment with a selective proteasome inhibitor, VELCADE, in combination with tissue plasminogen activator (tPA) extended the therapeutic window to 6 hours in young rats after stroke. However, stroke is a major cause of death and disability in the elderly. The present study investigated the effect of VELCADE in combination with a low-dose tPA on aged rats after embolic stroke. **METHODS:** Male Wistar rats at the age of 18 to 20 months were treated with VELCADE (0.2 mg/kg) alone, a low-dose tPA (5 mg/kg) alone, combination of VELCADE and tPA, or saline 2 hours after embolic middle cerebral artery

occlusion. To test the contribution of endothelial nitric oxide synthase to VELCADE-mediated neuroprotection, endothelial nitric oxide synthase knockout and wild-type mice were treated with VELCADE (0.5 mg/kg) 2 hours after embolic stroke. RESULTS: Treatment with VELCADE significantly reduced infarct volume, whereas tPA alone did not reduce infarct volume and aggravated blood-brain barrier disruption in aged rats compared with saline-treated rats. However, the combination treatment significantly enhanced the reduction of infarct volume, which was associated with an increase in endothelial nitric oxide synthase activity compared with saline-treated rats. Additionally, the combination treatment promoted thrombolysis and did not increase the incidence of hemorrhage transformation. VELCADE significantly reduced lesion volume in wild-type mice but failed to significantly reduce lesion volume in endothelial nitric oxide synthase knockout mice. CONCLUSIONS: Treatment with VELCADE exerts a neuroprotective effect in aged rats after stroke. The combination of VELCADE with the low-dose tPA further amplifies the neuroprotective effect. Endothelial nitric oxide synthase at least partly contributes to VELCADE-mediated neuroprotection after stroke.

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## Neurosurgery

Chang, V., H. Goshgarian, M. Simoff and J. Rock (2010). "Chronic Cough in an Adult Patient With Chiari Type-I Malformation." Neurosurgery Quarterly **20**(1): 27-30. [PDF Full-Text](#)

[Chang, Victor; Rock, Jack] Henry Ford Hosp, Dept Neurosurg, Detroit, MI 48202 USA. [Simoff, Michael] Henry Ford Hosp, Dept Pulm Med, Detroit, MI 48202 USA. [Goshgarian, Harry] Wayne State Univ, Sch Med, Dept Anat & Cell Biol, Detroit, MI 48201 USA.

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Objective and Importance: We report on a patient who had a chronic cough as the sole symptom of a Chiari I malformation that resolved with posterior fossa decompression. Clinical Presentation: The patient was earlier diagnosed with Chiari I malformation and underwent posterior fossa decompression. She subsequently developed a chronic cough that was not explained by an extensive pulmonary work-up. Intervention or Technique: The patient underwent reoperation, and the earlier suboccipital craniectomy was broadened by 2 cm. In addition, a tonsillectomy with dissection of arachnoid adhesions was also carried out, exposing the obex. A wide pericranial graft of the craniocervical junction was also carried out. Conclusions: The patient's cough resolved after reoperation. We speculate that the pathophysiology of her case may stem from irritation or compression of the cough re. ex circuitry in the dorsal medulla. This case represents an unusual manifestation of symptoms from a Chiari I malformation.

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## Neurosurgery

DeCarvalho, A. C., K. Nelson, N. Lemke, N. L. Lehman, A. S. Arbab, S. Kalkanis and T. Mikkelsen (2010). "Gliosarcoma Stem Cells Undergo Glial and Mesenchymal Differentiation In Vivo." Stem Cells **28**(2): 181-190. [PDF Full-Text](#)

[DeCarvalho, Ana C.] Henry Ford Hosp, Dept Neurosurg, Hermelin Brain Tumor Ctr, Detroit, MI 48202 USA. [Lehman, Norman L.] Henry Ford Hosp, Dept Pathol, Detroit, MI 48202 USA. [Arbab, Ali S.] Henry Ford Hosp, Dept Radiol, Detroit, MI 48202 USA. [Mikkelsen, Tom] Henry Ford Hosp, Dept Neurol, Detroit, MI 48202 USA. DeCarvalho, AC, Henry Ford Hosp, Dept Neurosurg, Hermelin Brain Tumor Ctr, E&R 3052,2799 W Grand Blvd, Detroit, MI 48202 USA. [ana@neuro.hfh.edu](mailto:ana@neuro.hfh.edu)

Cancer stem cells (CSCs) are characterized by their self-renewing potential and by their ability to differentiate and phenocopy the original tumor in orthotopic xenografts. Long-term propagation of glioblastoma (GBM) cells in serum-containing medium results in loss of the CSCs and outgrowth of cells genetically and biologically divergent from the parental tumors. In contrast, the use of a neurosphere assay, a serum-free culture for selection, and propagation of central nervous system-derived stem cells allows the selection of a subpopulation containing CSCs. Gliosarcoma (GS), a morphological variant comprising approximately 2% of GBMs, present a biphasic growth pattern, composed of glial and metaplastic mesenchymal components. To assess whether the neurosphere assay would allow the amplification of a subpopulation of cells with "gliosarcoma stem cell" properties, capable of propagating both components of this malignancy, we have generated neurospheres and serum cultures from primary GS and GBM surgical specimens. Neurosphere cultures from GBM and GS samples expressed neural stem cell markers Sox2, Musashi1, and Nestin. In

contrast to the GBM neurosphere lines, the GS neurospheres were negative for the stem cell marker CD133. All neurosphere lines generated high-grade invasive orthotopic tumor xenografts, with histological features strikingly similar to the parental tumors, demonstrating that these cultures indeed are enriched in CSCs. Remarkably, low-passage GS serum cultures retained the expression of stem cell markers, the ability to form neurospheres, and tumorigenicity. The GS experimental tumors phenocopied the parental tumor, exhibiting biphasic glial and mesenchymal components, constituting a clinically relevant model to investigate mesenchymal differentiation in GBMs. *STEM CELLS* 2009; 28:181-190

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## Neurosurgery

Jenrow, K. A., S. L. Brown, J. G. Liu, A. Kolozsvary, K. Lapanowski and J. H. Kim (2010). "Ramipril mitigates radiation-induced impairment of neurogenesis in the rat dentate gyrus." *Radiation Oncology* 5. [PDF Full-Text](#)

[Jenrow, Kenneth A.] Henry Ford Hosp, Dept Neurosurg, Detroit, MI 48202 USA. [Brown, Stephen L.; Liu, Jianguo; Kolozsvary, Andrew; Lapanowski, Karen; Kim, Jae Ho] Henry Ford Hosp, Dept Radiat Oncol, Detroit, MI 48202 USA.

Jenrow, KA, Henry Ford Hosp, Dept Neurosurg, 3074 E&R Bldg, 2799 W Grand Blvd, Detroit, MI 48202 USA. [nskje@neuro.hfh.edu](mailto:nskje@neuro.hfh.edu)

Background: Sublethal doses of whole brain irradiation (WBI) are commonly administered therapeutically and frequently result in late delayed radiation injuries, manifesting as severe and irreversible cognitive impairment. Neural progenitors within the subgranular zone (SGZ) of the dentate gyrus are among the most radiosensitive cell types in the adult brain and are known to participate in hippocampal plasticity and normal cognitive function. These progenitors and the specialized SZG microenvironment required for neuronal differentiation are the source of neurogenic potential in the adult dentate gyrus, and provide a continuous supply of immature neurons which may then migrate into the adjacent granule cell layer to become mature granule cell neurons. The extreme radiosensitivity of these progenitors and the SGZ microenvironment suggests the hippocampus as a prime target for radiation-induced cognitive impairment. The brain renin-angiotensin system (RAS) has previously been implicated as a potent modulator of neurogenesis within the SGZ and selective RAS inhibitors have been implicated as mitigators of radiation brain injury. Here we investigate the angiotensin converting enzyme (ACE) inhibitor, ramipril, as a mitigator of radiation injury in this context. Methods: Adult male Fisher 344 rats received WBI at doses of 10 Gy and 15 Gy. Ramipril was administered beginning 24 hours post-WBI and maintained continuously for 12 weeks. Results: Ramipril produced small but significant reductions in the deleterious effects of radiation on progenitor proliferation and neuronal differentiation in the rat dentate gyrus following 10 Gy-WBI, but was not effective following 15 Gy-WBI. Ramipril also reduced the basal rate of neurogenesis within the SGZ in unirradiated control rats. Conclusions: Our results indicate that chronic ACE inhibition with ramipril, initiated 24 hours post-irradiation, may reduce apoptosis among SGZ progenitors and/or inflammatory disruption of neurogenic signaling within SGZ microenvironment, and suggest that angiotensin II may participate in maintaining the basal rate of granule cell neurogenesis.

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## Neurosurgery

Kalkanis, S. N. and M. E. Linskey (2010). "Evidence-based clinical practice parameter guidelines for the treatment of patients with metastatic brain tumors: introduction." *J Neurooncol* 96(1): 7-10. 2808533. [PDF Full-Text](#)

Department of Neurosurgery, Henry Ford Health System, 2799 West Grand Blvd, K-11, Detroit, MI 48202, USA. [kalkanis@neuro.hfh.edu](mailto:kalkanis@neuro.hfh.edu)

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## Neurosurgery

Seyfried, D. M., Y. Han, D. Yang, J. Ding, L. H. Shen, S. Savant-Bhonsale and M. Chopp (2010). "Localization of bone marrow stromal cells to the injury site after intracerebral hemorrhage in rats." *J Neurosurg* 112(2): 329-35. 2833967. [PDF Full-Text](#)

Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan, USA.

**OBJECT:** Previous studies demonstrated that intravascular injection of bone marrow stromal cells (BMSCs) significantly improved neurological functional recovery in a rat model of intracerebral hemorrhage (ICH). To further investigate the fate of transplanted cells, we examined the effect of male rat BMSCs administered to female rats after ICH. **METHODS:** Twenty-seven female Wistar rats were subjected to ICH surgery. At 24 hours after ICH, these rats were randomly divided into 3 groups and injected intravenously with 1 ml phosphate-buffered saline or 0.5 million or 1 million male rat BMSCs in phosphate-buffered saline. To evaluate the neurological functional outcome, each rat was subjected to a series of behavioral tests (modified neurological severity score and corner turn test) at 1, 7, and 14 days after ICH. The rats were anesthetized intraperitoneally and killed, and the brain tissues were processed at Day 14 after ICH. Immunohistochemistry and in situ hybridization were used to identify cell-specific markers. **RESULTS:** The male rat BMSCs significantly improved the neurological functional outcome and also significantly diminished tissue loss when intravenously transplanted into the rats after ICH. Immunoassay for bromodeoxyuridine (BrdU) and neuronal markers demonstrated a significant increase in the number of BrdU-positive cells, which indicated endogenous neurogenesis, and a significant increase in the number of cells positive for immature neuronal markers. In situ hybridization showed that more BMSCs resided around the hematoma of the rats treated with the 1-million-cell dose compared with the 0.5-million-cell-dose group. In addition, a subfraction of Y chromosome-positive cells were co-immunostained with the neuronal marker microtubule-associated protein-2 or the astrocytic marker glial fibrillary acidic protein. **CONCLUSIONS:** Male rat BMSCs improve neurological outcome and increase histochemical parameters of neurogenesis when administered to female rats after ICH. This study has shown that the intravenously administered male rat BMSCs enter the brain, migrate to the perihematoma area, and express parenchymal markers.

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## Neurosurgery

Wen, P. Y., D. R. Macdonald, D. A. Reardon, T. F. Cloughesy, A. G. Sorensen, E. Galanis, J. Degroot, W. Wick, M. R. Gilbert, A. B. Lassman, C. Tsien, T. Mikkelsen, E. T. Wong, M. C. Chamberlain, R. Stupp, K. R. Lamborn, M. A. Vogelbaum, M. J. van den Bent and S. M. Chang (2010). "Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group." *J Clin Oncol* **EPub Ahead of Print**. [PDF Full-Text](#)

Center for Neuro-Oncology, Dana-Farber/Brigham and Women's Cancer Center; Division of Neurology, Brigham and Women's Hospital; Department of Radiology, Massachusetts General Hospital; Brain Tumor Center, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA; Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC; Neuro-Oncology Program, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles; Division of Neuro-Oncology, Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA; Department of Medical Oncology, Mayo Clinic, Rochester, MN; Department of Neuro-Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX; Department of Neurology and Brain Tumor Center, Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Radiation Oncology, University of Michigan Medical Center, Ann Arbor; Department of Neuro-Oncology, Henry Ford Hospital, Detroit, MI; Fred Hutchinson Cancer Center, Seattle, WA; Brain Tumor and Neuro-Oncology Center, Department of Neurosurgery, Cleveland Clinic, Cleveland OH; Department of Medical Oncology, London Regional Cancer Program, University of Western Ontario, London, Ontario, Canada; Department of Neuro-Oncology, University of Heidelberg, Heidelberg, Germany; Centre Hospitalier Universitaire Vaudois; University of Lausanne, Lausanne, Switzerland; and Neuro-Oncology Unit, Daniel den Hoed Cancer Center/Erasmus University Hospital, Rotterdam, the Netherlands.

Currently, the most widely used criteria for assessing response to therapy in high-grade gliomas are based on two-dimensional tumor measurements on computed tomography (CT) or magnetic resonance imaging (MRI), in conjunction with clinical assessment and corticosteroid dose (the Macdonald Criteria). It is increasingly apparent that there are significant limitations to these criteria, which only address the contrast-enhancing component of the tumor. For example, chemoradiotherapy for newly diagnosed glioblastomas results in transient increase in tumor enhancement (pseudoprogression) in 20% to 30% of patients, which is difficult to differentiate from true tumor progression. Antiangiogenic agents produce high radiographic response rates, as defined by a rapid decrease in contrast enhancement on CT/MRI that occurs within days of initiation of treatment and that is partly a result of reduced vascular permeability to contrast agents rather than a true antitumor effect. In addition, a subset of patients treated with antiangiogenic agents develop tumor recurrence characterized by an increase in the nonenhancing component depicted on T2-weighted/fluid-attenuated inversion recovery sequences. The recognition that contrast enhancement is nonspecific and may not always

be a true surrogate of tumor response and the need to account for the nonenhancing component of the tumor mandate that new criteria be developed and validated to permit accurate assessment of the efficacy of novel therapies. The Response Assessment in Neuro-Oncology Working Group is an international effort to develop new standardized response criteria for clinical trials in brain tumors. In this proposal, we present the recommendations for updated response criteria for high-grade gliomas.

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## Neurosurgery

Wu, H., H. Jiang, D. Lu, Y. Xiong, C. Qu, D. Zhou, A. Mahmood and M. Chopp (2009). "Effect of simvastatin on glioma cell proliferation, migration, and apoptosis." Neurosurgery **65**(6): 1087-96; discussion 1096-7. [PDF Full-Text](#)

Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan 48202, USA.

**OBJECTIVE:** In this study, we investigated the effects of simvastatin on proliferation, migration, and apoptosis in human U251 and U87 glioma cells and the underlying molecular mechanism. **METHODS:** We used colony formation assay to test the cell proliferation, in vitro scratch assay to examine the cell migration, and caspase-3 activity assay, annexin V staining, and cytochrome C release to evaluate the cell apoptosis. Lipid raft fractions were isolated from glioma cells. Total cholesterol content assay was used to test the change of cholesterol level in lipid raft fractions. Immunocytochemistry staining was performed to detect the changes of lipid rafts in cell membranes. Western blotting analysis was performed to examine the signal transduction both in cells and in lipid raft fractions. **RESULTS:** Simvastatin inhibited proliferation and migration of U251 and U87 cells dose dependently. Simvastatin induced an increase of caspase-3 activity and annexin V staining, and down-regulated the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. Simvastatin also decreased cholesterol content in lipid raft fractions, suppressed caveolin-1 expression in the lipid rafts, and induced Fas translocation into lipid rafts, suggesting that simvastatin may inhibit the prosurvival PI3K/Akt pathway and trigger caspase-3-dependent apoptotic cell death through the modulation of lipid rafts. **CONCLUSION:** These results suggest that modulation of lipid rafts, Fas translocation, and PI3K/Akt/caspase-3 pathway are involved in the antitumor effect of simvastatin and may have a potential role in cancer prevention and treatment.

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## Obstetrics & Gynecology

George, A., D. Eisenstein and G. Wegienka (2009). "Analysis of the impact of body mass index on the surgical outcomes after robot-assisted laparoscopic myomectomy." J Minim Invasive Gynecol **16**(6): 730-3. [PDF Full-Text](#)

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**STUDY OBJECTIVE:** To estimate the impact of body mass index (BMI) on surgical outcomes in patients undergoing robotic myomectomy. **DESIGN:** A retrospective cohort data analysis (Canadian Task Force classification II-2). **SETTING:** Community-based teaching hospital. **PATIENTS:** A total of 77 consecutive patients from January 2005 through November 2008 with symptomatic leiomyomata. **INTERVENTION:** Robotic-assisted laparoscopic myomectomy. **MEASUREMENTS AND MAIN RESULTS:** Body mass index ([BMI] expressed as kg/m<sup>2</sup>) was abstracted from the medical charts of all patients undergoing robotic myomectomy. Data on estimated blood loss, procedure time, length of hospital stay, diameter of the largest fibroid, and specimen weight were also extracted. Overall patient demographics between the groups were similar. Thirty-two patients (41.6%) were obese or morbidly obese (BMI>30). The parameters analyzed for associations with the continuous measure of BMI included length of postoperative hospital stay (LOS), estimated blood loss (EBL), and procedure duration. Median (range) procedure time among all patients was (195 minutes, 98-653 minutes), estimated blood loss was (100 mL, 10-700 mL), and length of hospital stay was (1 day, 1-5 days). No associations were determined between BMI and LOS ( $r=0.14$ ,  $p=.22$ ), EBL ( $r=0.25$ ,  $p=.03$ ), or procedure duration ( $r=0.16$ ,  $p=.22$ ) with Spearman correlations. The size of the largest leiomyoma diameter did not affect these associations. **CONCLUSION:** Preoperative obesity is not a risk factor for poor surgical outcome in patients undergoing robotic myomectomy.

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## Pharmacy

Winegardner, M. L., S. L. Davis, E. G. Szandzik and J. S. Kalus (2010). "Nontraditional pharmacy residency at a large teaching hospital." Am J Health Syst Pharm **67**(5): 366-70. [PDF Full-Text](#)

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**PURPOSE:** The structure and implementation of a nontraditional pharmacy residency program in a large teaching hospital are described. **SUMMARY:** A nontraditional track of the postgraduate year 1 (PGY1) residency program at a large teaching hospital in Detroit, Michigan, was developed for clinical staff pharmacists employed by the hospital. The program, accredited by the American Society of Health-System Pharmacists, allows pharmacists to complete 10 four-week rotations, in addition to three longitudinal rotations, over a three-year period. Required four-week rotations include 1 orientation rotation, 6 adult medicine rotations, 1 intensive care unit rotation, and 2 elective rotations. Because a pharmacist must first be employed by the hospital before applying to the nontraditional residency program, a staff pharmacist position is used to fund the nontraditional residency program. Since the inception of the nontraditional PGY1 residency program in 2005, two residents have graduated from the program. After completion of the residency, the first resident remained at the institution as a clinical staff pharmacist. The current and recently graduated nontraditional residents have demonstrated significant advancement of their clinical skills as a result of their participation in the program. Challenges faced during program implementation included scheduling and coordinating the resident's rotations and activities. **CONCLUSION:** A three-year nontraditional residency program was developed at a large teaching hospital to provide an alternative method for enhancing a pharmacist's clinical practice skills beyond those of an entry-level practitioner through completion of a systematic training program.

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### **Radiation Oncology**

Brown, S. L., A. Kolozsvar, J. Liu, K. A. Jenrow, S. Ryu and J. H. Kim (2010). "Antioxidant diet supplementation starting 24 hours after exposure reduces radiation lethality." Radiat Res **173**(4): 462-8. [PDF Full-Text](#)

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Antioxidants mitigate radiation-induced lethality when started soon after radiation exposure, a delivery time that may not be practical due to difficulties in distribution and because the oral administration of such agents may require a delay beyond the prodromal stage of the radiation syndrome. We report the unexpected finding that antioxidant supplementation starting 24 h after total-body irradiation resulted in better survival than antioxidant supplementation started soon after the irradiation. The antioxidant dietary supplement was l-selenomethionine, sodium ascorbate, N-acetyl cysteine, alpha-lipoic acid, alpha-tocopherol succinate, and co-enzyme Q10. Total-body irradiation with 8 Gy in the absence of antioxidant supplementation was lethal by day 16. When antioxidant supplementation was started soon after irradiation, four of 14 mice survived. In contrast, 14 of 18 mice receiving antioxidant supplementation starting 24 h after irradiation were alive and well 30 days later. The numbers of spleen colonies and blood cells were higher in mice receiving antioxidant supplementation starting 24 h after irradiation than in mice receiving radiation alone. A diet supplemented with antioxidants administered starting 24 h after total-body irradiation improved bone marrow cell survival and mitigated lethality, with a radiation protection factor of approximately 1.18.

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### **Radiation Oncology**

Huang, Y. M., M. Joiner, B. Zhao, Y. X. Liao and J. Burmeister (2010). "Dose convolution filter: Incorporating spatial dose information into tissue response modeling." Medical Physics **37**(3): 1068-1074. [Article Request Form](#)

[Huang, Yimei; Joiner, Michael; Zhao, Bo; Liao, Yixiang; Burmeister, Jay] Wayne State Univ, Karmanos Canc Ctr, Detroit, MI 48202 USA.

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**Methods:** The model consists of a dose convolution filter (DCF) with single parameter sigma. Tissue response is calculated by an existing NTCP model with DCF-applied dose distribution as input. The authors determined sigma of rat spinal cord from published data. The authors also simulated the GRID technique, in which an

open field is collimated into many pencil beams. Results: After applying the DCF, the NTCP model successfully fits the rat spinal cord data with a predicted value of  $\sigma=2.6 \pm 0.5$  mm, consistent with 2 mm migration distances of remyelinating cells. Moreover, it enables the appropriate prediction of a high relative seriality for spinal cord. The model also predicts the sparing of normal tissues by the GRID technique when the size of each pencil beam becomes comparable to  $\sigma$ . Conclusions: The DCF model incorporates spatial dose information and offers an improved way to estimate tissue response from complex radiotherapy dose distributions. It does not alter the prediction of tissue response in large homogenous fields, but successfully predicts increased tissue tolerance in small or highly nonuniform fields.

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## Radiation Oncology

Jin, J. Y., F. M. Kong, I. J. Chetty, M. Ajlouni, S. Ryu, R. Ten Haken and B. Movsas (2010). "Impact of fraction size on lung radiation toxicity: hypofractionation may be beneficial in dose escalation of radiotherapy for lung cancers." *Int J Radiat Oncol Biol Phys* **76**(3): 782-8. [PDF Full-Text](#)

Department of Radiation Oncology, Henry Ford Hospital, Detroit, MI 48202, USA. [jjin1@hfhs.org](mailto:jjin1@hfhs.org)

**PURPOSE:** To assess how fraction size impacts lung radiation toxicity and therapeutic ratio in treatment of lung cancers. **METHODS AND MATERIALS:** The relative damaged volume (RDV) of lung was used as the endpoint in the comparison of various fractionation schemes with the same normalized total dose (NTD) to the tumor. The RDV was computed from the biologically corrected lung dose-volume histogram (DVH), with an alpha/beta ratio of 3 and 10 for lung and tumor, respectively. Two different (linear and S-shaped) local dose-effect models that incorporated the concept of a threshold dose effect with a single parameter D(L50) (dose at 50% local dose effect) were used to convert the DVH into the RDV. The comparison was conducted using four representative DVHs at different NTD and D(L50) values. **RESULTS:** The RDV decreased with increasing dose/fraction when the NTD was larger than a critical dose (D(CR)) and increased when the NTD was less than D(CR). The D(CR) was 32-50 Gy and 58-87 Gy for a small tumor (11 cm<sup>3</sup>) for the linear and S-shaped local dose-effect models, respectively, when D(L50) was 20-30 Gy. The D(CR) was 66-97 Gy and 66-99 Gy, respectively, for a large tumor (266 cm<sup>3</sup>). Hypofractionation was preferred for small tumors and higher NTDs, and conventional fractionation was better for large tumors and lower NTDs. Hypofractionation might be beneficial for intermediate-sized tumors when NTD = 80-90 Gy, especially if the D(L50) is small (20 Gy). **CONCLUSION:** This computational study demonstrated that hypofractionated stereotactic body radiotherapy is a better regimen than conventional fractionation in lung cancer patients with small tumors and high doses, because it generates lower RDV when the tumor NTD is kept unchanged.

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## Radiation Oncology

Ryu, S., J. Rock, R. Jain, M. Lu, J. Anderson, J. Y. Jin, M. Rosenblum, B. Movsas and J. H. Kim (2010). "Radiosurgical decompression of metastatic epidural compression." *Cancer EPub Ahead of Print*. [PDF Full-Text](#)

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**BACKGROUND::** Surgical decompression of metastatic epidural compression (MEC) improved ambulatory function. Spine radiosurgery can accurately target the epidural tumor and deliver high radiation doses for tumor control. Therefore, a clinical trial was performed to quantitatively determine the degree of epidural decompression by radiosurgery of metastatic epidural compression. **METHODS::** Sixty-two patients with a total of 85 lesions of metastatic epidural compression were treated. Epidural compression was diagnosed by magnetic resonance imaging (MRI) scans. Main criteria of inclusion were neurological status with muscle power 4 of 5 or better. Radiosurgery was performed to the involved spine segment, including the epidural mass with median dose of 16 Gy (range 12-20 Gy) in a single session. All patients had prospective clinical follow-up, ranging from 1-48 months (median 11.5 months), and 36 patients had pretreatment and post-treatment imaging, ranging from 2-33 months (median 9.3 months). Primary endpoints were epidural tumor control and thecal sac decompression. **RESULTS::** The mean epidural tumor volume reduction was 65 +/- 14% at 2 months after radiosurgery. The epidural tumor area at the level of the most severe spinal cord compression was 0.82 +/- 0.08 cm<sup>2</sup> before radiosurgery and 0.41 +/- 0.06 cm<sup>2</sup> after radiosurgery (P < .001). Thecal sac patency improved from 55 +/- 4% to 76 +/- 3% (P < .001). Overall, neurological function improved in 81%. **CONCLUSIONS::** This study demonstrated a radiosurgical decompression of epidural tumor.

Although neurosurgical decompression and radiotherapy is the standard treatment in patients with good performance, radiosurgical decompression can be a viable noninvasive treatment option for malignant epidural compression. Cancer 2010. (c) 2010 American Cancer Society.

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### **Radiation Oncology**

Yan, C., H. Zhong, M. Murphy, E. Weiss and J. V. Siebers (2010). "A pseudoinverse deformation vector field generator and its applications." Medical Physics **37**(3): 1117-1128.

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[Yan, C.; Zhong, H.; Murphy, M.; Weiss, E.; Siebers, J. V.] Virginia Commonwealth Univ, Dept Radiat Oncol, Richmond, VA 23298 USA. [Zhong, H.] Henry Ford Hlth Syst, Dept Radiat Oncol, Detroit, MI 48202 USA. Yan, C, Virginia Commonwealth Univ, Dept Radiat Oncol, POB 980058, Richmond, VA 23298 USA. [cyan@mcvh-vcu.edu](mailto:cyan@mcvh-vcu.edu)

Methods: The algorithm is an iterative scheme based on nearest neighbor interpolation and a subsequent iterative search. Performance of the algorithm is benchmarked using a lung 4DCT data set with six CT images from different breathing phases and eight CT images for a single prostate patient acquired on different days. A diffeomorphic deformable image registration is used to validate our PIDVFs. Additionally, the PIDVF is used to measure the self-consistency of two nondiffeomorphic algorithms which do not use a self-consistency constraint: The ITK Demons algorithm for the lung patient images and an in-house B-Spline algorithm for the prostate patient images. Both Demons and B-Spline have been QAed through contour comparison. Self-consistency is determined by using a DIR to generate a displacement vector field (DVF) between reference image R and study image S (DVFR-S). The same DIR is used to generate DVFS-R. Additionally, our PIDVF generator is used to create PIDVFS-R. Back-and-forth mapping of a set of points (used as surrogates of contours) using DVFR-S and DVFS-R is compared to back-and-forth mapping performed with DVFR-S and PIDVFS-R. The Euclidean distances between the original unmapped points and the mapped points are used as a self-consistency measure. Results: Test results demonstrate that the consistency error observed in back-and-forth mappings can be reduced two to nine times in point mapping and 1.5 to three times in dose mapping when the PIDVF is used in place of the B-Spline algorithm. These self-consistency improvements are not affected by the exchanging of R and S. It is also demonstrated that differences between DVFS-R and PIDVFS-R can be used as a criteria to check the quality of the DVF. Conclusions: Use of DVF and its PIDVF will improve the self-consistency of points, contour, and dose mappings in image guided adaptive therapy.

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### **Radiation Oncology**

Zhong, H. L., J. Kim and I. J. Chetty (2010). "Analysis of deformable image registration accuracy using computational modeling." Medical Physics **37**(3): 970-979. [Article Request Form](#)

#### [Form](#)

[Zhong, Hualiang; Kim, Jinkoo; Chetty, Indrin J.] Henry Ford Hlth Syst, Dept Radiat Oncol, Detroit, MI 48202 USA.

Zhong, HL, Henry Ford Hlth Syst, Dept Radiat Oncol, Detroit, MI 48202 USA. [hzhong1@hfhs.org](mailto:hzhong1@hfhs.org)

Computer aided modeling of anatomic deformation, allowing various techniques and protocols in radiation therapy to be systematically verified and studied, has become increasingly attractive. In this study the potential issues in deformable image registration (DIR) were analyzed based on two numerical phantoms: One, a synthesized, low intensity gradient prostate image, and the other a lung patient's CT image data set. Each phantom was modeled with region-specific material parameters with its deformation solved using a finite element method. The resultant displacements were used to construct a benchmark to quantify the displacement errors of the Demons and B-Spline-based registrations. The results show that the accuracy of these registration algorithms depends on the chosen parameters, the selection of which is closely associated with the intensity gradients of the underlying images. For the Demons algorithm, both single resolution (SR) and multiresolution (MR) registrations required approximately 300 iterations to reach an accuracy of 1.4 mm mean error in the lung patient's CT image (and 0.7 mm mean error averaged in the lung only). For the low gradient prostate phantom, these algorithms (both SR and MR) required at least 1600 iterations to reduce their mean errors to 2 mm. For the B-Spline algorithms, best performance (mean errors of 1.9 mm for SR and 1.6 mm for MR, respectively) on the low gradient prostate was achieved using five grid nodes in each direction. Adding more grid nodes resulted in larger errors. For the lung patient's CT data set, the B-Spline registrations

required ten grid nodes in each direction for highest accuracy (1.4 mm for SR and 1.5 mm for MR). The numbers of iterations or grid nodes required for optimal registrations depended on the intensity gradients of the underlying images. In summary, the performance of the Demons and B-Spline registrations have been quantitatively evaluated using numerical phantoms. The results show that parameter selection for optimal accuracy is closely related to the intensity gradients of the underlying images. Also, the result that the DIR algorithms produce much lower errors in heterogeneous lung regions relative to homogeneous (low intensity gradient) regions, suggests that feature-based evaluation of deformable image registration accuracy must be viewed cautiously.

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## Sleep Medicine

Randall, S., C. E. Johanson, M. Tancer and T. Roehrs (2009). "Effects of acute 3,4-methylenedioxymethamphetamine on sleep and daytime sleepiness in MDMA users: a preliminary study." *Sleep* **32**(11): 1513-9. 2768958. [PDF Full-Text](#)

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**STUDY OBJECTIVE:** 3,4-Methylenedioxymethamphetamine (MDMA) affects monoamine neurotransmitters that play a critical role in sleep and daytime alertness. However, the acute effects of MDMA on sleep and daytime sleepiness have not been studied under placebo-controlled conditions. This study was designed to establish the effects of acute MDMA or placebo administration and sleep restriction on sleep and daytime sleepiness. **DESIGN:** Participants with a history of MDMA use were studied on 3 sessions of 3 nights (baseline, treatment, and recovery) and 2 days (following night 2 and 3) per session. On treatment nights (night 2), participants received placebo or 2 mg/kg of MDMA or underwent a restricted bed schedule with placebo. Sleep restriction was a positive control to compare sleep loss and consequent sleepiness associated with MDMA use. The scheduled sleep period was 8 hours long on nonrestricted nights, and standard sleep recordings and daytime sleepiness tests were conducted. Age-matched controls received 1 night and day of standard sleep and daytime sleepiness testing. **SETTING:** Sleep laboratory. **PARTICIPANTS:** Seven recreational MDMA-users and 13 matched control subjects. **MEASUREMENTS AND RESULTS:** Acute MDMA shortened sleep primarily by increasing sleep latency, and it reduced stage 3/4 sleep and suppressed rapid eye movement (REM) sleep. The MDMA-reduced sleep time was not associated with increased daytime sleepiness the following day, as was seen in the sleep-restriction condition. Compared with control subjects, the MDMA users on the first night in the laboratory had shorter total sleep times and less stage 3/4 sleep. Average daily sleep latency on daytime sleepiness tests the day after nighttime placebo administration was increased in MDMA users compared with the control subjects, and MDMA users had an elevated number of sleep-onset REM periods on these tests, compared with control subjects. **CONCLUSIONS:** Acute MDMA administration disrupts sleep and REM sleep, specifically, without producing daytime sleepiness such as sleep restriction does. Compared with control subjects, recreational MDMA users showed evidence of hyperarousal and impaired REM function. The mechanism behind these effects is likely due to the deleterious effects of MDMA on catecholamines.

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## Sleep Medicine

Roth, T., C. Lines, K. Vandormael, P. Ceesay, D. Anderson and D. Snavely (2010). "Effect of gaboxadol on patient-reported measures of sleep and waking function in patients with Primary Insomnia: results from two randomized, controlled, 3-month studies." *J Clin Sleep Med* **6**(1): 30-9. 2823273. [PDF Full-Text](#)

Henry Ford Hospital Sleep Disorders and Research Center, Detroit, MI, USA.

**OBJECTIVE:** To evaluate the efficacy and safety of gaboxadol in the treatment of Primary Insomnia. **METHODS:** Two studies were performed in patients 18 to 65 years of age with Primary Insomnia. After a 7-day single-blind placebo run-in, patients were randomized to double-blind treatment with gaboxadol 15 mg (N = 310), 10 mg (N = 308), or placebo (N = 309) over 3 months in Study 1; and gaboxadol 15 mg (N = 304) or placebo (N = 301) over 12 months in Study 2. Treatment was administered at bedtime. The primary efficacy endpoints in each study were change from baseline in patient-reported total sleep time (sTST) and time to sleep onset (sTSO) at month 3. Safety was assessed primarily by adverse event reports. **RESULTS:** In Study 1, gaboxadol 15 mg significantly improved sTST (difference vs. placebo of 20.4 min,  $p < 0.01$ ) and sTSO

(difference vs. placebo of -9.8 min,  $p < 0.05$ ) at 3 months, while gaboxadol 10 mg had no significant effects on these measures. In Study 2, gaboxadol 15 mg showed numerical superiority for improvements on sTST (difference vs. placebo of 14.5 min) and sTSO (difference vs. placebo of -4.9 min) at 3 months, but these differences were not significant. In both studies, there was evidence that the efficacy of gaboxadol was more pronounced in women than men. Gaboxadol was generally well tolerated over 3 months in Study 1, and over 12 months in Study 2. **CONCLUSION:** Gaboxadol 15 mg showed variable efficacy on measures of sleep duration and onset at 3 months in adult patients with Primary Insomnia in these studies and appeared to be more effective in women than men. Gaboxadol 10 mg was not effective in these studies. (Clinical trial registration numbers: NCT00103818, NCT00095069).

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## **Surgery**

Benninger, M. S., K. McFarlin, D. R. Hamilton, I. Rubinfeld, A. E. Sargsyan, S. M. Melton, M. Mohyi and S. A. Dulchavsky (2009). "Ultrasound evaluation of sinus fluid levels in swine during microgravity conditions." *Aviat Space Environ Med* **80**(12): 1063-5. [Article Request Form](#)

Department of Surgery, CFP-1, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI 48202, USA.

**BACKGROUND:** Acute rhinosinusitis is a common problem that could occur in space secondary to absence of gravity-dependent drainage or odontogenic or external sources of infection. The purpose of this study was to determine the efficacy of ultrasound to determine sinus fluid distribution levels in swine and to assess the accuracy of ultrasound in the animal during normal and microgravity conditions. **METHODS:** Anesthetized swine had a catheter placed through a frontal bone window to allow aliquots of a viscous solution to be injected at 1 G ( $N = 4$ ) or during brief microgravity parabolic flights ( $N = 4$ ). Ultrasound examinations were performed with a high frequency probe during baseline and fluid-induced conditions. **RESULTS:** There was a consistent air-fluid level interface seen on ultrasound examination with the injection of 1 ml of fluid during 1-G conditions. Microgravity conditions caused the rapid ( $< 10$  s) dissolution of the air-fluid level associated with dispersion of the fluid to the walls of the sinus cavity in a uniform fashion. The air-fluid interface was recreated with return to 1 G. **CONCLUSIONS:** Ultrasound is a reliable diagnostic test for assessing fluid levels; these experiments demonstrate the technique can be used during microgravity conditions with attention to altered fluid behavior in the absence of gravity.

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## **Surgery**

Kakkos, S. K., G. K. Haddad, M. R. Weaver, R. K. Haddad and M. M. Scully (2010). "Basilic Vein Transposition: What is the Optimal Technique?" *Eur J Vasc Endovasc Surg* **EPub Ahead of Print**. [Article Request Form](#)

Division of Vascular Surgery, Department of Surgery, Henry Ford Hospital, K-8, 2799 W. Grand Boulevard, Detroit, MI 48202, USA.

**OBJECTIVES:** To compare the outcome of the one-stage basilic vein transposition (BVT) fistula with a modified, two-stage technique. **DESIGN:** Retrospective case-controlled study, performed in an academic centre. **MATERIAL:** A total of 173 candidates for BVT fistula (87 males, mean age 61 years). **METHODS:** In one-stage BVT, the basilic vein is mobilised through a single incision, placed inside an anterolateral arm tunnel and anastomosed with the brachial artery. In two-stage procedures, the fistula-arterial anastomosis is created first, followed by the second stage, after fistula maturation several weeks later, when the basilic vein is mobilised through two skip incisions, transected near the anastomosis, placed inside an anterolateral arm tunnel and reanastomosed. Morbidity and fistula maturation rate were the main outcome measures. **RESULTS:** In one-stage BVT ( $n=76$ ), the incidence of venous hypertension, wound haematomas and all complications (17%, 13% and 43%, respectively) was significantly higher than in two-stage procedures ( $n=98$ ) (4%,  $p=0.004$ , 3%,  $p=0.012$  and 11%,  $p<0.001$ , respectively). Time (68 days) to fistula use was significantly decreased in one-stage BVT than in two-stage procedures (132 days,  $p<0.001$ ) but failure to mature rate was equivalent (15% vs. 18%,  $p=0.49$ ). **CONCLUSIONS:** Our results indicate that the two-stage BVT fistula through two skip-arm incisions is superior to the established one-stage procedure in terms of less morbidity but at the cost of a second operation and longer time to access use. Further research comparing these two techniques is necessary. Until this issue is resolved, an individualised approach is suggested.

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## **Surgery**

Otto, C., J. M. Comtois, A. Sargsyan, A. Dulchavsky, I. Rubinfeld and S. Dulchavsky (2010). "The Martian chronicles: remotely guided diagnosis and treatment in the arctic circle." [Surg Endosc EPub Ahead of Print](#). [PDF Full-Text](#)

Emergency Medicine, University of Ottawa, Ottawa, ON, Canada.

**BACKGROUND:** Despite rigorous health screening in astronaut crews, there are a number of conditions that may occur during long duration, exploration class spaceflight. The risk of abdominal conditions requiring surgical intervention is not clear, yet submarine and polar base experiences suggest contingency planning is warranted. While radio communication time delay is only 2 s to the international space station (ISS), a potential Mars mission would necessitate time delays of about 15 min. We sought to demonstrate the feasibility of remote expert guidance of diagnostic ultrasound followed by laparoscopic appendectomy in a simulated Mars environment. **METHODS:** Research was deemed exempt by the institutional review board. A simulated Mars research environment was utilized on Devon Island in the Canadian Arctic. Electronic communications including audio and video were established between the Arctic base and Henry Ford Hospital serving as Mission Control and incorporated the 15-min communications lag into all communication. Ultrasound and laparoscopic capabilities were integrated into communications for remote guidance. Remote guidance methods and technology utilized has been previously published in communication with the ISS. A simulated scenario involving a young female astronaut developing right lower quadrant pain was developed and utilized for this demonstration. An anatomical appendectomy model was utilized for the ultrasound and laparoscopic portions. Reference aids describing background technical aspects were developed. A set of confirmation milestones was used to generate a hard stop and mandated remote review. **RESULTS:** The simulated appendectomy was successfully pursued on the first attempt with no delays or untoward events. Reference aids were appropriate for non-surgical personnel and hard stops for milestones with remote approval and go ahead were shown to be feasible. The appendicitis was appropriately diagnosed utilizing remote guidance of ultrasonography and the appendix removed laparoscopically using stapled technique with remote guidance as well. **CONCLUSIONS:** We report a successful remote guidance demonstration from a simulated Mars environment with clinical control from a terrestrial base utilizing appropriate delay and consistent bandwidth and technology.

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## **Surgery**

Parker, A., I. Rubinfeld, O. Azuh, D. Blyden, A. Falvo, M. Horst, V. Velanovich and P. Patton (2010). "What ring tone should be used for patient safety? Early results with a Blackberry-based telementoring safety solution." [Am J Surg](#) **199**(3): 336-40; discussion 340-1. [PDF Full-Text](#)

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**OBJECTIVE:** Technology currently exists for the application of remote guidance in the laparoscopic operating suite. However, these solutions are costly and require extensive preparation and reconfiguration of current hardware. We propose a solution from existing technology, to send video of laparoscopic cholecystectomy to the Blackberry Pearl device (RIM Waterloo, ON, Canada) for remote guidance purposes. This technology is time- and cost-efficient, as well as reliable. **METHODS:** After identification of the critical maneuver during a laparoscopic cholecystectomy as the division of the cystic duct, we captured a segment of video before it's transection. Video was captured using the laparoscopic camera input sent via DVI2USB Solo Frame Grabber (Epiphan Ottawa, Canada) to a video recording application on a laptop. Seven- to 40-second video clips were recorded. The video clip was then converted to an .mp4 file and was uploaded to our server and a link was then sent to the consultant via e-mail. The consultant accessed the file via Blackberry for viewing. After reviewing the video, the consultant was able to confidently comment on the operation. **RESULTS:** Approximately 7 to 40 seconds of 10 laparoscopic cholecystectomies were recorded and transferred to the consultant using our method. All 10 video clips were reviewed and deemed adequate for decision making. **CONCLUSION:** Remote guidance for laparoscopic cholecystectomy with existing technology can be accomplished with relatively low cost and minimal setup. Additional evaluation of our methods will aim to identify reliability, validity, and accuracy. Using our method, other forms of remote guidance may be feasible, such as other laparoscopic procedures, diagnostic ultrasonography, and remote intensive care unit monitoring.

In addition, this method of remote guidance may be extended to centers with smaller budgets, allowing ubiquitous use of neighboring consultants and improved safety for our patients.

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## **Surgery**

Siddiqui, A. and D. Tepper (2010). "Muscle flap arterialization by means of negative-pressure wound therapy." Plast Reconstr Surg **125**(2): 89e. [PDF Full-Text](#)

Division of Plastic Surgery; Henry Ford Hospital, Detroit, Mich 48230, USA. [asiddiq1@hfhs.org](mailto:asiddiq1@hfhs.org)

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## **Surgery**

Williams, J., A. Hodari, P. Janevski and A. Siddiqui (2010). "Recurrence of giant cell tumors in the hand: a prospective study." J Hand Surg Am **35**(3): 451-6. [PDF Full-Text](#)

Henry Ford Hospital, Detroit, MI 48202, USA.

**PURPOSE:** Giant cell tumors of the hand remain a treatment dilemma: treatment requires a balance between extensive dissections for excision versus risk of recurrence. There is no consensus regarding how best to manage this balance. The purpose of this study was to identify the recurrence rate of giant cell tumors of the hand, as well as the correlation with the specific tissue type involved. **METHODS:** Two hundred thirteen cases of giant cell tumor of the hand were recorded in a prospectively designed, anatomically based registry that identified tumor location and surgical planes entered and tissues excised during the procedure. Mean follow-up was 51 months. Demographic and follow-up data were also tracked. The primary outcome tracked was tumor recurrence. Statistical analysis was conducted using chi-square analysis and the Fisher exact test to determine which perioperative and intraoperative factors were associated with tumor recurrence. **RESULTS:** There were 27 recurrences among our cases. Tumors involving the extensor tendon, flexor tendon, or joint capsule had the strongest correlation with recurrence: 12, 8, and 12 cases, respectively. Conversely, there was only one recurrence among the patients who did not have any involvement of either the flexor or extensor tendons or joint capsules. There was no association for involvement of skin, neurovascular bundle, tendon sheath, or bone at the initial excision. No identifiable preoperative or postoperative factors were linked to recurrence. **CONCLUSIONS:** Our study shows that direct involvement of the extensor tendons, flexor tendons, or joint capsule puts patients in a high-risk category with respect to recurrence. Based on these findings, efforts regarding close monitoring and the role of adjuvant therapy should be directed at the high-risk population. This information may be helpful for hand surgeons developing evidence-based treatment algorithms for giant cell tumor in the hand. **TYPE OF STUDY/LEVEL OF EVIDENCE:** Prognostic III.

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## **Urology**

Benway, B. M., S. B. Bhayani, C. G. Rogers, J. R. Porter, N. M. Buffi, R. S. Figenshau and A. Mottrie (2010). "Robot-Assisted Partial Nephrectomy: An International Experience." European Urology **57**(5): 815-820. [PDF Full-Text](#)

[Benway, Brian M.; Bhayani, Sam B.; Figenshau, Robert S.] Washington Univ, Sch Med, Dept Surg, Div Urol Surg, St Louis, MO 63110 USA. [Rogers, Craig G.] Henry Ford Hosp, Vattikuti Urol Inst, Detroit, MI 48202 USA. [Porter, James R.] Swedish Urol Grp, Seattle, WA USA. [Buffi, Nicolo M.] Univ Vita Salute San Raffaele, Dept Urol, San Raffaele Turro Hosp, Milan, Italy. [Mottrie, Alexandre] Onze Lieve Vrouw Hosp, Dept Urol, Aalst, Belgium.

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[benwayb@wudosis.wustl.edu](mailto:benwayb@wudosis.wustl.edu)

**Background:** Robot-assisted partial nephrectomy (RAPN) is emerging as a viable approach for nephron-sparing surgery (NSS), though many reports to date have been limited by evaluation of a relatively small number of patients. **Objective:** We present the largest multicenter RAPN experience to date, culling data from four high-volume centers, with focus upon functional and oncologic outcomes. **Design, setting, and participants:** A retrospective chart review was performed for 183 patients who underwent RAPN at four centers between 2006 and 2008. **Surgical procedure:** RAPN was performed using methods outlined in the supplemental video material. Though operative technique was similar across all institutions, there were minor

variations in trocar placement and hilar control. Measurements: Perioperative parameters, including operative time, warm ischemic time, blood loss, and perioperative complications were recorded. In addition, we reviewed functional and oncologic outcomes. Results and limitations: Mean age at treatment was 59.3 yr. Mean tumor size was 2.87 cm. Mean total operative time was 210 min while mean ischemic time was 23.9 min. Calyceal repair was required in 52.1% of procedures. Mean estimated blood loss was 131.5 ml. Sixty-nine percent of excised tumors were malignant, of which 2.7% exhibited positive surgical margins. The incidence of major complications was 8.2%. At up to 26 mo follow-up, there have been no documented recurrences and no significant change in serum creatinine (1.03 vs 1.04 mg/dl,  $p = 0.84$ ) or estimated glomerular filtration rate (eGFR) from baseline (82.2 vs 79.4 mg/ml per square meter,  $p = 0.74$ ). The study is limited by its retrospective nature, and the outcomes are likely influenced by the robust prior laparoscopic renal experience of each of the surgeons included in this study. Conclusions: RAPN is a safe and efficacious approach for NSS, offering short ischemic times, as well as perioperative morbidity equivalent to other standard approaches. Moreover, RAPN is capable of providing patients with excellent functional and oncologic outcomes. (C) 2010 European Association of Urology. Published by Elsevier B. V. All rights reserved.

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## Urology

Bhandari, A., O. Alassi, C. Rogers and G. T. Maclennan (2010). "Squamous Cell Carcinoma of the Renal Pelvis." J Urol **Epub Ahead of Print**. [PDF Full-Text](#)

Vattikuti Urology Institute and Department of Pathology, Henry Ford Health System, Detroit, Michigan.

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## Urology

Koroukian, S. M., F. Xu, P. M. Bakaki, M. Diaz-Insua, T. P. Towe and C. Owusu (2010). "Comorbidities, Functional Limitations, and Geriatric Syndromes in Relation to Treatment and Survival Patterns Among Elders With Colorectal Cancer." Journals of Gerontology Series a-Biological Sciences and Medical Sciences **65**(3): 322-329. [PDF Full-Text](#)

[Koroukian, Siran M.; Xu, Fang; Bakaki, Paul M.] Case Western Reserve Univ, Sch Med, Dept Epidemiol & Biostat, Cleveland, OH 44106 USA. [Koroukian, Siran M.; Towe, Tanyanika Phillips; Owusu, Cynthia] Case Comprehens Canc Ctr, Canc Aging Program, Cleveland, OH USA. [Diaz-Insua, Mireya] Henry Ford Hosp, Vattikuti Urol Inst, Detroit, MI 48202 USA. [Towe, Tanyanika Phillips; Owusu, Cynthia] Univ Hosp Cleveland, Dept Internal Med, Div Hematol & Oncol, Cleveland, OH 44106 USA.

Koroukian, SM, Case Western Reserve Univ, Sch Med, Dept Epidemiol & Biostat, 10900 Euclid Ave, Cleveland, OH 44106 USA. [skoroukian@case.edu](mailto:skoroukian@case.edu)

Purpose. To examine patterns of colorectal cancer (CRC) treatment and survival in relation to comorbidities (COM), functional limitations (FL), and geriatric syndromes (GS). Methods. Our Study population consisted of Ohio elders diagnosed with incident invasive CRC in the period August 1999 to November 2001 and admitted to home health care (HHC) in the 30 days before or after cancer diagnosis ( $n = 1009$ ). We used data from the Ohio Cancer Incidence Surveillance System, vital records, and Medicare administrative data, including the HHC Outcome and Assessment Information Set (OASIS), which includes detailed clinical data for HHC patients. Counts of COM, FL, and GS at baseline were retrieved from the OASIS. Multivariable logistic and survival models were developed to examine the association between clinical attributes and outcomes, adjusting for demographic covariates and cancer stage. Results. Comorbidities were associated with increased likelihood of surgery-only, but not with surgery + chemotherapy. Both FL and GS were associated with lower likelihood to undergo surgery-only or surgery + chemotherapy. Two or more GS was associated with disease-specific mortality (adjusted hazard ratio [AHR]: 2.71; 95% confidence interval [CI]: 1.80-4.07) and overall mortality (AHR: 2.34; 95% CI: 1.74-3.15). Two or more FL was associated with overall mortality (AHR: 1.33; 95% CI: 1.10-1.62), but not with disease-specific mortality. COM was not associated with overall mortality, but was negatively associated with disease-specific mortality at borderline level of significance (AHR: 0.78 95% CI: 0.61-1.00). Conclusion. Our findings demonstrate the importance of accounting for FL and GS, in addition to COM, when studying cancer-related outcomes in elders.

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## Urology

Mansour, A. M., S. J. Marshall, E. D. Arnone, S. A. Seixas-Mikelus, A. Hussain, H. Abol-Enein, J. O. Peabody and K. A. Guru (2010). "Status of robot-assisted radical cystectomy." Canadian Journal of Urology **17**(1): 5002-5011. [Article Request Form](#)

[Mansour, Ahmed M.; Marshall, Susan J.; Arnone, Eric D.; Seixas-Mikelus, Stefanie A.; Hussain, Abid; Guru, Khurshid A.] SUNY Buffalo, Roswell Pk Canc Inst, Dept Urol Oncol, Buffalo, NY 14263 USA. [Mansour, Ahmed M.; Abol-Enein, Hassan] Mansoura Univ, Urol & Nephrol Ctr, Mansoura, Egypt. [Peabody, James O.] Henry Ford Hosp, Vattikuti Urol Inst, Detroit, MI 48202 USA.

Guru, KA, SUNY Buffalo, Roswell Pk Canc Inst, Dept Urol Oncol, Elm & Carlton Str, Buffalo, NY 14263 USA.

Purpose: Robot-assisted radical cystectomy (RARC) is an alternative approach for treatment of bladder cancer. We provide a critical review of the current status of RARC and pelvic lymph node dissection with a focus on feasibility, safety and oncological efficacy of the procedure. Materials and methods: The PubMed literature database was reviewed for RARC series that have been reported in the English language until the present time. Surgical technique, operative parameters, pathologic outcome, complications and quality of life were examined. Results: RARC is progressing steadily. With nearly 500 published cases worldwide, RARC proves to be technically feasible and oncologically effective. It is associated with less blood loss, shorter hospital stay, and improved postoperative quality of life. Intracorporeal urinary diversion is still in the experimental phase, and effort is needed to make it technically easier and widely accepted. Conclusions: With the worldwide rapid spread of robot-assisted surgeries, RARC is evolving as a reliable minimally invasive alternative to standard open surgery. Awaiting long term oncological results, adequately powered prospective randomized trials comparing open, laparoscopic and robotic approaches are urgently needed.

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