

## Henry Ford Health System Publication List - January 2010

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### **Biostatistics & Research Epidemiology**

Divine, G., A. Kapke, S. Havstad and C. L. M. Joseph (2010). "Exemplary data set sample size calculation for Wilcoxon-Mann-Whitney tests." Statistics in Medicine **29**(1): 108-115. [Article Request Form](#)

[Divine, George; Kapke, Alissa; Havstad, Suzanne; Joseph, Christine L. M.] Henry Ford Hosp, Dept Biostat & Res Epidemiol, Detroit, MI 48202 USA. Divine, G, Henry Ford Hosp, Dept Biostat & Res Epidemiol, 1 Ford Pl,3E, Detroit, MI 48202 USA. [gdivine1@hfhs.org](mailto:gdivine1@hfhs.org)

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 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. Copyright (C) 2009 John Wiley & Sons, Ltd.

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### **Biostatistics & Research Epidemiology**

Yood, M. U., P. F. Wang, Z. Zhao, S. H. Alford, S. Oliveria, K. Wells, S. Phillips, H. Ali and C. O'Malley (2009). "Treatment-related toxicities in patients with squamous cell carcinoma of the head and neck (SCCHN)." Ejc Supplements **7**(2): 477-477. [Article Request Form](#)

[Yood, M. Ulcickas; Oliveria, S.; Phillips, S.] EpiSource LLC, Hamden, CT USA. [Wang, P. Feng; Zhao, Z.; O'Malley, C.] Amgen Inc, Global Epidemiol, Thousand Oaks, CA USA. [Alford, S. Hensley; Wells, K.] Henry Ford Hlth Syst, Biostat & Res Epidemiol, Detroit, MI USA. [Ali, H.] Henry Ford Med Grp, Detroit, MI USA.

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### **Bone & Joint Center**

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8:30am-7:30pm M-Th  
8:30am-5:00pm F

Bonifasi-Lista, C., E. Cherkaev and Y. N. Yeni (2009). "Analytical Approach to Recovering Bone Porosity From Effective Complex Shear Modulus." Journal of Biomechanical Engineering-Transactions of the Asme **131**(12). [Article Request Form](#)

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This work deals with the study of the analytical relations between porosity of cancellous bone and its mechanical properties. The Stieltjes representation of the effective shear complex modulus of cancellous bone is exploited to recover porosity. The microstructural information is contained in the spectral measure in this analytical representation. The spectral function can be recovered from the effective measurements over a range of frequencies. The problem of reconstruction of the spectral measure is very ill-posed. Regularized algorithm is derived to ensure stability of the results. The proposed method does not use any specific assumptions about the microgeometry of bone. The approach does not rely on correlation analysis, it uses analytical relationships. For validation purposes, complex shear modulus over a range of frequencies was calculated by the finite element method using micro-computed tomography (micro-CT) images of human cancellous bone. The calculated values were used in numerical algorithm to recover bone porosity. At the microlevel, bone was modeled as a heterogeneous medium composed of trabeculae tissue and bone marrow treated as transversely isotropic elastic and isotropic viscoelastic materials, respectively. Recovered porosity values are in excellent agreement with true porosity found from the corresponding micro-CT images. [DOI: 10.1115/1.4000082]

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### **Bone & Joint Center**

Nelson, F. R. and N. Hay (2008). "Ethical safeguards for industry-funded research in an academic setting." J Long Term Eff Med Implants **18**(2): 175-9. [Article Request Form](#)

Henry Ford Hospital, Dearborn, MI 48202, USA. [nelson@bjc.hfh.edu](mailto:nelson@bjc.hfh.edu)

The shrinking economy has driven many investigators to seek industrial funding for both clinical and bench research. This has resulted in four concerns for the clinician scientist: (1) research that results in effective clinical application; (2) research design that meets evidence medicine requirements and has clinical significance; (3) adherence to clinical competencies; and (4) research records that are open and reflect both the scientific and economic path to the results of the investigation. This paper reports on how one institution protects the interests of all four stakeholders in any research study in academic centers: the investigator, the institution, patients, and industry. The process makes it possible for the investigator to concentrate on research methodology and to remain secure about the ethical conduct of their research. At our institution, all industrial-funded research is arranged on an institution-to-sponsor basis. Contract language is generated by the institution, not the investigator. This protects the investigator and includes freedom to publish regardless of the results. Issues of intellectual property, patient protection, and the institutions needs, such as intellectual property and compliance with the federal/state guidelines, and indemnification are incorporated into the pre- and post-award applications. Concurrently, Institutional Review Board (IRB) proposals are prepared and submitted. This process leaves a paper trail that provides a transparency acceptable to all stakeholders.

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### **Bone & Joint Center**

Yeni, Y. N., X. N. Dong, B. Zhang, G. J. Gibson and D. P. Fyhrie (2009). "Cancellous bone properties and matrix content of TGF-beta2 and IGF-I in human tibia: a pilot study." Clin Orthop Relat Res **467**(12): 3079-86. 2772931. [PDF Full-Text](#)

Department of Orthopaedics and Rehabilitation, Section of Biomechanics, Bone and Joint Center, Henry Ford Hospital, 2799 West Grand Boulevard, E&R 2015, Detroit, MI 48202, USA. [yeni@bjc.hfh.edu](mailto:yeni@bjc.hfh.edu)

Transforming and insulin-like growth factors are important in regulating bone mass. Thus, one would anticipate correlations between matrix concentrations of growth factors and functional properties of bone. We therefore investigated the relationships of (1) TGF-beta2 and (2) IGF-I matrix concentrations with the trabecular

microstructure, stress distribution, and mechanical properties of tibial cancellous bone from six male human cadavers. Trabecular stress amplification (VMExp/sigma(app)) and variability (VMCOV) were calculated using microcomputed tomography (muCT)-based finite element simulations. Bone volume fraction (BV/TV), surface/volume ratio (BS/BV), trabecular thickness (Tb.Th), number (Tb.N) and separation (Tb.Sp), connectivity (Eu.N), and anisotropy (DA) were measured using 3-D morphometry. Bone stiffness and strength were measured by mechanical testing. Matrix concentrations of TGF-beta2 and IGF-I were measured by ELISA. We found higher matrix concentrations of TGF-beta2 were associated with higher Tb.Sp and VMExp/sigma(app) for pooled data and within subjects. Similarly, a higher matrix concentration of IGF-I was associated with lower stiffness, strength, BV/TV and Tb.Th and with higher BS/BV, Tb.Sp, VMExp/sigma(app) and VMCOV for pooled data and within subjects. IGF-I and Tb.N were negatively associated within subjects. It appears variations of the stress distribution in cancellous bone correlate with the variation of the concentrations of TGF-beta2 and IGF-I in bone matrix: increased local matrix concentrations of growth factors are associated with poor biomechanical and architectural properties of tibial cancellous bone.

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## **Bone & Joint Center**

Zhang, L., M. Yang, D. Yang, G. Cavey, P. Davidson and G. Gibson (2010). "Molecular Interactions of MMP-13 C-Terminal Domain with Chondrocyte Proteins." [Connect Tissue Res Epub Ahead of Print.](#) [Article Request Form](#)

Bone and Joint Center, Henry Ford Hospital, Detroit, Michigan, USA.

Matrix metalloproteinases (MMP)-13 activity is necessary for normal skeletal development and plays a central role in cartilage degeneration associated with osteoarthritis (OA). The studies we described here examine the interactions of the hemopexin domain of MMP-13 with proteins secreted by human chondrocytes in culture. The hemopexin domain of the MMPs and many other proteins in which this structure is found mediates protein function by forming the primary site of interaction with other proteins. We have modified a tandem affinity expression tag (hTAP) to enable efficient expression of the tagged bait protein. In this case the MMP-13 C-terminal domain (CTD) comprises hinge and hemopexin domain, and we immobilized the fusion construct on a column of agarose bound immunoglobulin G. The MMP-13 CTD affinity column so generated enabled the efficient and gentle isolation of interacting proteins from the culture medium of human articular chondrocytes. TIMP1 and alpha2-macroglobulin previously shown to interact with MMP-13 as well as several proteins, fibronectin, type VI collagen and xylosyltransferase 1 and several proteoglycans, decorin, syndecan 4 and serglycin not previously recognized as interacting with MMP-13 were identified by mass spectrometry. The interaction between isolated proteins and MMP-13 CTD was verified by yeast two hybrid analysis. We also demonstrated serglycin expression by chondrocytes for the first time and its co localization with MMP-13 in a cytoplasmic granular morphology. The consequence of these interactions remains to be demonstrated, however; binding to MMP-13 suggests a role in the regulation of cartilage degradation.

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## **Cardiology**

Alqaisi, F., L. K. Williams, E. L. Peterson and D. E. Lanfear (2009). "Comparing methods for identifying patients with heart failure using electronic data sources." [Bmc Health Services Research](#) **9**. [PDF Full-Text](#)

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Background: Accurately identifying heart failure (HF) patients from administrative claims data is useful for both research and quality of care efforts. Yet, there are few comparisons of the various claims data criteria (also known as claims signatures) for identifying HF patients. We compared various HF claim signatures to assess their relative accuracy. Methods: In this retrospective study, we identified 4174 patients who received care from a large health system in southeast Michigan and who had  $\geq 1$  HF encounter between January 1, 2004 and December 31, 2005. Four hundred patients were chosen at random and a detailed chart review was performed to assess which met the Framingham HF criteria. The sample was divided into 300 subjects for derivation and 100 subjects for validation. Sensitivity, specificity,, and area under the curve (AUC) were determined for the various claim signatures. The criteria with the highest AUC were retested in the validation

set. Results: Of the 400 patients sampled, 65% met Framingham HF criteria, and 56% had at least one B-type Natriuretic Peptide (BNP) measurement. There was substantial variation between claims signatures in terms of sensitivity (range 15%-77%) and specificity (range 69%-100%). The best performing criteria in the derivation set was if patients met any one of the following:  $\geq 2$  HF encounters, any hospital discharge diagnosis of HF, or a BNP  $\geq 200$  pg/ml. These criteria showed a sensitivity of 76%, specificity of 75%, and AUC of 0.754 for meeting the Framingham HF criteria. This claims signature performed similarly in the validation set. Conclusion: Claim signatures for HF vary greatly in their relative sensitivity and specificity. These findings may facilitate efforts to identify HF patients for research and quality improvement efforts.

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## Cardiology

Dhar, R., S. Bhojraj and M. H. Al-Mallah (2009). "Training in cardiovascular computer tomography: The Fellows-In-Training perspective." J Cardiovasc Comput Tomogr **EPub Ahead of Print**. [Article Request Form](#)

Henry Ford Hospital, 2799 West Grand Boulevard, K14, Detroit, MI 48202, USA.

BACKGROUND: Cardiovascular computed tomography angiography (CCTA) is an emerging diagnostic technique in the evaluation of patients with suspected coronary artery disease. The recent CoCATS guidelines recommend that all cardiovascular fellows be exposed to CCTA in their training programs; however, not all programs have the ability to provide such training. OBJECTIVE: This study aims to describe the present opinions of Fellows-in-Training (FIT) toward CCTA training. METHODS: Cardiovascular FITs in the state of Michigan were contacted through the American College of Cardiology, Michigan chapter, e-mail list and were asked to complete a 12-question anonymous survey examining attitudes toward CCTA. RESULTS: Sixty (54%) of 112 FITs completed the survey. Ninety-one percent of respondents had a CCTA program at their hospital and 52 (87%) considered CCTA important toward increasing their professional competitiveness. In addition, 93% had interest in obtaining at least level 2 training irrespective of their future career plans. The most important factors influencing their choice of third-party courses were cost, number of live cases, and student-to-faculty ratio. Finally, 47% supported creating an additional fourth year of training in advanced imaging, and 40% would pursue such training. CONCLUSION: Most cardiovascular FITs are interested in seeking advanced training in CCTA. Cardiovascular training programs should incorporate CCTA in their core curriculum to meet the increasing interest in CCTA among trainees.

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## Cardiology

Wenk, J. F., S. T. Wall, R. C. Peterson, S. L. Helgerson, H. N. Sabbah, M. Burger, N. Stander, M. B. Ratcliffe and J. M. Guccione (2009). "A Method for Automatically Optimizing Medical Devices for Treating Heart Failure: Designing Polymeric Injection Patterns." Journal of Biomechanical Engineering-Transactions of the Asme **131**(12). [Article Request Form](#)

[Ratcliffe, Mark B.; Guccione, Julius M.] Univ Calif San Francisco, Dept Surg, San Francisco, CA 94121 USA. [Ratcliffe, Mark B.; Guccione, Julius M.] San Francisco VA Med Ctr, San Francisco, CA 94121 USA. [Wenk, Jonathan F.; Wall, Samuel T.; Peterson, Robert C.; Helgerson, Sam L.] CardioPolymers Inc, Laguna Hills, CA 92653 USA. [Sabbah, Hani N.] Henry Ford Hlth Syst, Detroit, MI 48202 USA. [Burger, Mike; Stander, Nielen] Livermore Software Technol Corp, Livermore, CA 94550 USA. Guccione, JM, Univ Calif San Francisco, Dept Surg, San Francisco, CA 94121 USA. [guccionej@surgery.ucsf.edu](mailto:guccionej@surgery.ucsf.edu)

Heart failure continues to present a significant medical and economic burden throughout the developed world. Novel treatments involving the injection of polymeric materials into the myocardium of the failing left ventricle (LV) are currently being developed, which may reduce elevated myofiber stresses during the cardiac cycle and act to retard the progression of heart failure. A finite element (FE) simulation-based method was developed in this study that can automatically optimize the injection pattern of the polymeric "inclusions" according to a specific objective function, using commercially available software tools The FE preprocessor TRUEGRID (R) was used to create a parametric axisymmetric LV mesh matched to experimentally measured end-diastole and end-systole metrics from dogs with coronary microembolization-induced heart failure. Passive and active myocardial material properties were defined by a pseudo-elastic-strain energy function and a time-varying elastance model of active contraction, respectively, that were implemented in the FE software LS-DYNA. The companion optimization software LS-OPT was used to communicate directly with TRUEGRID (R) to determine FE model parameters, such as defining the injection pattern and inclusion characteristics. The optimization

resulted in an intuitive optimal injection pattern (i.e., the one with the greatest number of inclusions) when the objective function was weighted to minimize mean end-diastolic and end-systolic myofiber stress and ignore LV stroke volume. In contrast, the optimization resulted in a nonintuitive optimal pattern (i.e., 3 inclusions longitudinally x 6 inclusions circumferentially) when both myofiber stress and stroke volume were incorporated into the objective function with different weights. [DOI: 10.1115/1.4000165]

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## **Dermatology**

Mi, Q. S., S. L. Yan, Z. Z. Wang, K. H. Ding, C. G. Li, L. Wang, L. Zhou, Y. Yamamoto, H. Yamamoto, H. Okamoto and C. Isales (2009). "Spontaneous bone loss in RIP-iNOS transgenic mouse A mouse model for diabetes-mediated osteopenia/osteoporosis." Cell Cycle **8**(24): 4179-4181. [Article Request Form](#)

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## **Dermatology**

Tang, N., H. Gibson, T. Germeroth, P. Porcu, H. W. Lim and H. K. Wong (2010). "T-plastin (PLS3) gene expression differentiates Sezary syndrome from mycosis fungoides and inflammatory skin diseases and can serve as a biomarker to monitor disease progression." British Journal of Dermatology **162**(2): 463-466. [Article Request Form](#)

[Tang, N.; Gibson, H.; Germeroth, T.; Lim, H. W.] Henry Ford Hosp, Dept Dermatol, Detroit, MI 48202 USA. [Porcu, P.] Ohio State Univ, Ctr Comprehens Canc, Div Hematol & Oncol, Dept Internal Med, Columbus, OH 43210 USA. [Wong, H. K.] Ohio State Univ, Div Dermatol, Med Ctr, Columbus, OH 43210 USA. Wong, HK, Henry Ford Hosp, Dept Dermatol, Detroit, MI 48202 USA. [henry.wong@osumc.edu](mailto:henry.wong@osumc.edu)

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## **Diagnostic Radiology**

Ali, M. M., B. Janic, A. Babajani-Feremi, N. R. Varma, A. S. Iskander, J. Anagli and A. S. Arbab (2010). "Changes in vascular permeability and expression of different angiogenic factors following anti-angiogenic treatment in rat glioma." PLoS One **5**(1): e8727. 2806917. [PDF Full-Text](#)

Cellular and Molecular Imaging Laboratory, Department of Radiology, Henry Ford Hospital, Detroit, Michigan, United States of America.

**BACKGROUND:** Anti-angiogenic treatments of malignant tumors targeting vascular endothelial growth factor receptors (VEGFR) tyrosine kinase are being used in different early stages of clinical trials. Very recently, VEGFR tyrosine kinase inhibitor (Vetanalib, PTK787) was used in glioma patient in conjunction with chemotherapy and radiotherapy. However, changes in the tumor size, tumor vascular permeability, vascular density, expression of VEGFR2 and other angiogenic factors in response to PTK787 are not well documented. This study was to determine the changes in tumor size, vascular permeability, fractional plasma volume and expression of VEGFR2 in PTK787 treated U-251 glioma rat model by in vivo magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT). The findings were validated with histochemical and western blot studies. **METHODOLOGIES AND PRINCIPAL FINDINGS:** Seven days after implantation of U251 glioma cells, animals were treated with either PTK787 or vehicle-only for two weeks, and

then tumor size, tumor vascular permeability transfer constant ( $K(\text{trans})$ ), fractional plasma volume (fPV) and expression of VEGFR2 and other relevant angiogenic factors were assessed by in vivo MRI and SPECT (Tc-99m-HYNIC-VEGF), and by immunohistochemistry and western blot analysis. Dynamic contrast-enhanced MRI (DCE-MRI) using a high molecular weight contrast agent albumin-(GdDTPA) showed significantly increased  $K(\text{trans})$  at the rim of the treated tumors compared to that of the central part of the treated as well as the untreated (vehicle treated) tumors. Size of the tumors was also increased in the treated group. Expression of VEGFR2 detected by Tc-99m-HYNIC-VEGF SPECT also showed significantly increased activity in the treated tumors. In PTK787-treated tumors, histological staining revealed increase in microvessel density in the close proximity to the tumor border. Western blot analysis indicated increased expression of VEGF, SDF-1, HIF-1 $\alpha$ , VEGFR2, VEGFR3 and EGFR at the peripheral part of the treated tumors compared to that of central part of the treated tumors. Similar expression patterns were not observed in vehicle treated tumors. CONCLUSION: These findings indicate that PTK787 treatment induced over expression of VEGF as well as the Flk-1/VEGFR2 receptor tyrosine kinase, especially at the rim of the tumor, as proven by DCE-MRI, SPECT imaging, immunohistochemistry and western blot.

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## Diagnostic Radiology

Babajani-Feremi, A. and H. Soltanian-Zadeh (2010). "Multi-area neural mass modeling of EEG and MEG signals." Neuroimage **Epub Ahead of Print**. [Article Request Form](#)

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We previously proposed an integrated electroencephalography (EEG), magnetoencephalography (MEG), and functional Magnetic Resonance Imaging (fMRI) model based on an extended neural mass model (ENMM) within a single cortical area. In the ENMM, a cortical area contains several minicolumns where strengths of their connections diminish exponentially with their distances. The ENMM was derived based on the physiological principles of the cortical minicolumns and their connections within a single cortical area to generate EEG, MEG, and fMRI signals. The purpose of this paper is to further extend the ENMM model from a single-area to a multi-area model to develop a neural mass model of the entire brain that generates EEG and MEG signals. For multi-area modeling, two connection types are considered: short-range connections (SRCs) and long-range connections (LRCs). The intra-area SRCs among the minicolumns within the areas were previously modeled in the ENMM. To define inter-area LRCs among the cortical areas, we consider that the cell populations of all minicolumns in the destination area are affected by the excitatory afferent of the pyramidal cells of all minicolumns in the source area. The state-space representation of the multi-area model is derived considering the intra-minicolumn, SRCs', and LRCs' parameters. Using simulations, we evaluate effects of parameters of the model on its dynamics and, based on stability analysis, find valid ranges for parameters of the model. In addition, we evaluate reducing redundancy of the model parameters using simulation results and conclude that the parameters of the model can be limited to the LRCs and SRCs while the intra-minicolumn parameters stay at their physiological mean values. The proposed multi-area integrated E/MEG model provides an efficient neuroimaging technique for effective connectivity analysis in healthy subjects as well as neurological and psychiatric patients.

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## Diagnostic Radiology

Bijari, P. B., A. Akhondi-Asl and H. Soltanian-Zadeh (2009). "Three-dimensional coupled-object segmentation using symmetry and tissue type information." Comput Med Imaging Graph **Epub Ahead of Print**. [Article Request Form](#)

Control and Intelligent Processing Center of Excellence, Electrical and Computer Engineering Department, University of Tehran, Tehran, Iran; School of Cognitive Sciences, Institute for Studies in Theoretical Physics and Mathematics (IPM), Tehran, Iran.

This paper presents an automatic method for segmentation of brain structures using their symmetry and tissue type information. The proposed method generates segmented structures that have homogenous tissues. It benefits from general symmetry of the brain structures in the two hemispheres. It also benefits from the tissue regions generated by fuzzy c-means clustering. All in all, the proposed method can be described as a dynamic knowledge-based method that eliminates the need for statistical shape models of the structures while generating accurate segmentation results. The proposed approach is implemented in MATLAB and tested on the Internet Brain Segmentation Repository (IBSR) datasets. To this end, it is applied to the segmentation of

caudate and ventricles three-dimensionally in magnetic resonance images (MRI) of the brain. Impacts of each of the steps of the proposed approach are demonstrated through experiments. It is shown that the proposed method generates accurate segmentation results that are insensitive to initialization and parameter selection. The proposed method is compared to four previous methods illustrating advantages and limitations of each method.

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## Diagnostic Radiology

Janic, B., A. S. M. Iskander, A. M. Rad, H. Soltanian-Zadeh and A. S. Arbab (2008). "Effects of Ferumoxides - Protamine Sulfate Labeling on Immunomodulatory Characteristics of Macrophage-like THP-1 Cells." PLoS One 3(6). [PDF Full-Text](#)

Janic, B, Henry Ford Hosp, Dept Radiol, Cellular & Mol Imaging Lab, Detroit, MI 48202 USA.  
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Superparamagnetic Iron Oxide (SPIO) complexed with cationic transfection agent is used to label various mammalian cells. Labeled cells can then be utilized as an in vivo magnetic resonance imaging (MRI) probes. However, certain number of in vivo administered labeled cells may be cleared from tissues by the host's macrophages. For successful translation to routine clinical application of SPIO labeling method it is important that this mode of in vivo clearance of iron does not elicit any diverse immunological effects. The purpose of this study was to demonstrate that SPIO agent ferumoxides-protamine sulfate (FePro) incorporation into macrophages does not alter immunological properties of these cells with regard to differentiation, chemotaxis, and ability to respond to the activation stimuli and to modulate T cell response. We used THP-1 cell line as a model for studying macrophage cell type. THP-1 cells were magnetically labeled with FePro, differentiated with 100 nM of phorbol ester, 12-Myristate-13-acetate (TPA) and stimulated with 100 ng/ml of LPS. The results showed 1) FePro labeling had no effect on the changes in morphology and expression of cell surface proteins associated with TPA induced differentiation; 2) FePro labeled cells responded to LPS with slightly higher levels of NFkB pathway activation, as shown by immunoblotting; TNF-alpha secretion and cell surface expression levels of CD54 and CD83 activation markers, under these conditions, were still comparable to the levels observed in non-labeled cells; 3) FePro labeling exhibited differential, chemokine dependent, effect on THP-1 chemotaxis with a decrease in cell directional migration to MCP-1; 4) FePro labeling did not affect the ability of THP-1 cells to down-regulate T cell expression of CD4 and CD8 and to induce T cell proliferation. Our study demonstrated that intracellular incorporation of FePro complexes does not alter overall immunological properties of THP-1 cells. The described experiments provide the model for studying the effects of in vivo clearance of iron particles via incorporation into the host's macrophages that may follow after in vivo application of any type of magnetically labeled mammalian cells. To better mimic the complex in vivo scenario, this model may be further exploited by introducing additional cellular and biological, immunologically relevant, components.

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## Diagnostic Radiology

Janic, B., A. M. Rad, E. K. Jordan, A. S. M. Iskander, M. M. Ali, N. R. S. Varma, J. A. Frank and A. S. Arbab (2009). "Optimization and Validation of FePro Cell Labeling Method." PLoS One 4(6). [PDF Full-Text](#)

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Current method to magnetically label cells using ferumoxides (Fe)-protamine (Pro) sulfate (FePro) is based on generating FePro complexes in a serum free media that are then incubated overnight with cells for the efficient labeling. However, this labeling technique requires long (>12-16 hours) incubation time and uses relatively high dose of Pro (5-6 mu g/ml) that makes large extracellular FePro complexes. These complexes can be difficult to clean with simple cell washes and may create low signal intensity on T2\* weighted MRI that is not desirable. The purpose of this study was to revise the current labeling method by using low dose of Pro and adding Fe and Pro directly to the cells before generating any FePro complexes. Human tumor glioma (U251) and human monocytic leukemia cell (THP-1) lines were used as model systems for attached and suspension cell types, respectively and dose dependent (Fe 25 to 100 mu g/ml and Pro 0.75 to 3 mu g/ml) and time dependent (2 to 48 h) labeling experiments were performed. Labeling efficiency and cell viability of these cells were assessed. Prussian blue staining revealed that more than 95% of cells were labeled. Intracellular iron

concentration in U251 cells reached similar to 30-35 pg-iron/cell at 24 h when labeled with 100 mu g/ml of Fe and 3 mu g/ml of Pro. However, comparable labeling was observed after 4 h across the described FePro concentrations. Similarly, THP-1 cells achieved similar to 10 pg-iron/cell at 48 h when labeled with 100 mu g/ml of Fe and 3 mu g/ml of Pro. Again, comparable labeling was observed after 4 h for the described FePro concentrations. FePro labeling did not significantly affect cell viability. There was almost no extracellular FePro complexes observed after simple cell washes. To validate and to determine the effectiveness of the revised technique, human T-cells, human hematopoietic stem cells (hHSC), human bone marrow stromal cells (hMSC) and mouse neuronal stem cells (mNSC C17.2) were labeled. Labeling for 4 hours using 100 mu g/ml of Fe and 3 mu g/ml of Pro resulted in very efficient labeling of these cells, without impairing their viability and functional capability. The new technique with short incubation time using 100 mu g/ml of Fe and 3 mu g/ml of Pro is effective in labeling cells for cellular MRI.

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## Diagnostic Radiology

Mahmoudi, S. E., A. Akhondi-Asl, R. Rahmani, S. Faghih-Roohi, V. Taimouri, A. Sabouri and H. Soltanian-Zadeh (2009). "Web-based interactive 2D/3D medical image processing and visualization software." Comput Methods Programs Biomed **Epub Ahead of Print.**

[Article Request Form](#)

Control and Intelligent Processing Center of Excellence (CIPCE), School of Electrical and Computer Engineering, University of Tehran, Tehran, Iran.

There are many medical image processing software tools available for research and diagnosis purposes. However, most of these tools are available only as local applications. This limits the accessibility of the software to a specific machine, and thus the data and processing power of that application are not available to other workstations. Further, there are operating system and processing power limitations which prevent such applications from running on every type of workstation. By developing web-based tools, it is possible for users to access the medical image processing functionalities wherever the internet is available. In this paper, we introduce a pure web-based, interactive, extendable, 2D and 3D medical image processing and visualization application that requires no client installation. Our software uses a four-layered design consisting of an algorithm layer, web-user-interface layer, server communication layer, and wrapper layer. To compete with extendibility of the current local medical image processing software, each layer is highly independent of other layers. A wide range of medical image preprocessing, registration, and segmentation methods are implemented using open source libraries. Desktop-like user interaction is provided by using AJAX technology in the web-user-interface. For the visualization functionality of the software, the VRML standard is used to provide 3D features over the web. Integration of these technologies has allowed implementation of our purely web-based software with high functionality without requiring powerful computational resources in the client side. The user-interface is designed such that the users can select appropriate parameters for practical research and clinical studies.

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## Diagnostic Radiology

Moghaddam, M. J. and H. Soltanian-Zadeh (2009). "Automatic segmentation of brain structures using geometric moment invariants and artificial neural networks." Inf Process Med Imaging **21**: 326-37. [Article Request Form](#)

Control and Intelligent Processing Center of Excellence, Department of Electrical and Computer Engineering, University of Tehran, Tehran, Iran. [m.jabaruti@ece.ut.ac.ir](mailto:m.jabaruti@ece.ut.ac.ir)

We propose an automatic method for the segmentation of the brain structures in three dimensional (3D) Magnetic Resonance Images (MRI). The proposed method consists of two stages. In the first stage, we represent the shape of the structure using Geometric Moment Invariants (GMIs) in 8 scales. For each scale, an Artificial Neural Network (ANN) is designed to approximate the signed distance function of a desired structure. The GMIs along with the voxel intensities and coordinates are used as the input features of the ANN and the signed distance function as its output. In the second stage, we combine the outputs of the ANNs of the first stage and design another ANN to classify the image voxels into two classes, inside or outside of the structure. We introduce a fast method for moment calculations. The proposed method is applied to the segmentation of caudate, putamen, and thalamus in MRI where it has outperformed other methods in the literature.

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## Diagnostic Radiology

Mohammadi-Nejad, A. R., G. A. Hossein-Zadeh and H. Soltanian-Zadeh (2010). "Quantitative evaluation of optimal imaging parameters for single-cell detection in MRI using simulation." Magn Reson Imaging **EPub Ahead of Print**. [PDF Full-Text](#)

Control and Intelligent Processing Center of Excellence, School of Electrical and Computer Engineering, University of Tehran, Tehran, Iran.

Super-paramagnetic iron oxide (SPIO) nanoparticles are actively investigated to enhance disease detection through molecular imaging using magnetic resonance imaging (MRI). Detection of the cells labeled by SPIO depends on the MRI protocols and pulse sequence parameters that can be optimized. To evaluate the sensitivity and specificity of the image acquisition methods and to obtain optimal imaging parameters for single-cell detection, we further developed an MRI simulator. The simulator models an object (tissue) at a microscopic level to evaluate effects of spatial distribution and concentration of nanoparticles on the resulting image. In this study, the simulator was used to evaluate and compare imaging of the labeled cells by the gradient-echo (GE), true-FISP [fast imaging employing steady-state acquisition (FIESTA)] and echo-planar imaging (EPI) pulse sequences. Effects of the imaging and object parameters, such as field strength, imaging protocol and pulse sequence parameters, imaging resolution, cell iron load, position of SPIO within the voxel and cell division within the voxel, were investigated in the work. The results suggest that true-FISP has the highest sensitivity for single-cell detection by MRI.

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## Diagnostic Radiology

Nazem-Zadeh, M. R., E. Davoodi-Bojd and H. Soltanian-Zadeh (2009). "Level set fiber bundle segmentation using spherical harmonic coefficients." Comput Med Imaging Graph **EPub Ahead of Print**. [Article Request Form](#)

Control and Intelligent Processing Center of Excellence, School of Electrical and Computer Engineering, University of Tehran, Tehran 14395-515, Iran.

Classifying brain white matter fibers into bundles is of growing interest in neuroscience. Quantification of diffusion characteristics inside a fiber bundle provides new insights for disease evolutions, therapy effects, and surgical interventions. In this paper, we present a novel method for segmenting fiber bundles using spherical harmonic coefficients (SHC) that describe diffusion signal obtained from High Angular Resolution Diffusion Imaging (HARDI) protocols. Based on SHC, we define a similarity measure and use it as a speed function term in level set framework. We show advantages of the proposed measure over similarity measures based on Diffusion Tensor Imaging (DTI) indices. Without any assumptions about diffusion model, we deal with diffusion signal instead of orientation distribution function (ODF) calculated using complicated mathematics, inaccurate simplifications, and time-consuming implementation. By applying the proposed algorithm on synthetic data, its superior accuracy and robustness in low SNR conditions are shown. Application of the proposed method on real HARDI MRI data also illustrates its superior performance, especially in heterogeneous diffusion areas with low traditional diffusion anisotropies.

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## Diagnostic Radiology

Shepard, S. J., J. H. Wang, M. Flynn, E. Gingold, L. Goldman, K. Krugh, D. L. Leong, E. Mah, K. Ogden, D. Peck, E. Samei and C. E. Willis (2010). "An exposure indicator for digital radiography: AAPM Task Group 116, Executive Summary (vol 36, pg 2898, 2009)." Medical Physics **37**(1): 405-405. [Article Request Form](#)

[Shepard, S. Jeff; Wang, Jihong; Wang, Jihong] Univ Texas MD Anderson Canc Ctr, Dept Imaging Phys, Div Diagnost Imaging, Houston, TX 77030 USA. [Flynn, Michael] Henry Ford Hlth Syst, Dept Radiol, Detroit, MI 48202 USA. [Gingold, Eric] Thomas Jefferson Univ Hosp, Dept Radiol, Philadelphia, PA 19107 USA. [Goldman, Lee] Hartford Hosp, Dept Med Phys, Hartford, CT 06102 USA. [Krugh, Kerry] Toledo Hosp, Dept Radiol, Toledo, OH 43606 USA. [Leong, David L.] Analogic Corp, Peabody, MA 01960 USA. [Mah, Eugene] Med Univ S Carolina, Dept Radiol, Charleston, SC 29425 USA. [Ogden, Kent] SUNY Upstate Med Univ, Dept Radiol, Syracuse, NY 13210 USA. [Peck, Donald] Henry Ford Hosp, Detroit, MI 48202 USA. [Samei, Ehsan]

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### **Drug Discovery & Development**

Shaw, J., F. A. Valeriote, J. Media, T. A. Johnson, T. Amagata, K. Tenney and P. Crews (2009). "Development and validation of a rapid method for the detection of latrunculol A in plasma." Anal Bioanal Chem **EPub Ahead of Print**. [PDF Full-Text](#)

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Latrunculol A is a recently discovered 6,7-dihydroxy analog of the potent actin inhibitor latrunculin A. Latrunculol A has exhibited greater cytotoxicity than latrunculin A against both murine and human colon tumor cell lines in vitro. Currently, there are no reports regarding the bioavailability of latrunculol A in vivo. This study was undertaken as a prelude to pharmacokinetic assessments and it is the first work where bioavailability of latrunculol A was studied. In the present work, a simple plasma preparation and a rapid HPLC method have been developed. Mouse plasma containing latrunculol A was first treated by acetonitrile and then centrifuged at 14,000 rpm at 4 degrees C for 25 min. The supernatant was injected in an HPLC system comprising a Waters Symmetry NH(2) column, a mobile phase of acetonitrile/water (95/5, v/v), a flow rate of 1.0 mL/min, at 220 nm. The method was validated by parameters including a good linear correlation, a limit of quantification of 9 ng/mL, and a good precision with a coefficient variation of 1.65, 1.86, and 1.26% for 20, 400, and 800 ng/mL, respectively. With this simple method, excellent separation and sensitivity of latrunculol A are achieved, thus allowing a rapid analysis of the plasma samples for absorption, distribution, and metabolism studies.

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### **Emergency Medicine**

Manteuffel, J. (2009). "Non-traumatic Shoulder Dislocation." West J Emerg Med **10(4)**: 304. 2791744. [PDF Full-Text](#)

Henry Ford Hospital, Department of Emergency Medicine, Detroit, MI.

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### **Endocrinology & Metabolism**

Bhadada, S. K., R. K. Padala, A. Bhansali, D. S. Rao and B. R. Mittal (2009). "Visual Vignette." Endocrine Practice **15(7)**: 767-767. [PDF Full-Text](#)

[Bhadada, Sanjay K.; Padala, Ravi K.; Bhansali, Anil] Postgrad Inst Med Educ & Res, Dept Endocrinol, Chandigarh 160012, India. [Mittal, Bhagwant R.] Postgrad Inst Med Educ & Res, Dept Nucl Med, Chandigarh 160012, India. [Rao, D. Sudhaker] Henry Ford Hlth Syst, Div Endocrinol & Metab, Detroit, MI USA. Bhansali, A, Postgrad Inst Med Educ & Res, Dept Endocrinol, Chandigarh 160012, India.  
[Anilbhansali\\_endocrine@rediffmail.com](mailto:Anilbhansali_endocrine@rediffmail.com)

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### **Endocrinology & Metabolism**

Hao, Y. Q., G. L. Hao, S. J. Qiu and B. S. Wang (2009). "Effects of age and gender on the likelihood of hip fracture in the elderly population in Shanghai, China." Saudi Medical Journal **30(11)**: 1483-1485. [Article Request Form](#)

[Hao, Yongqiang; Hao, Guangliang] Shanghai Jiao Tong Univ, Dept Orthoped Surg, Sch Med, Shanghai 200030, Peoples R China. [Wang, Bingshun] Shanghai Jiao Tong Univ, Peoples Hosp 9, Sch Med, Biol Stat Dept, Shanghai 200030, Peoples R China. [Qiu, Shijing] Henry Ford Hosp, Bone & Mineral Res Lab, Detroit, MI 48202 USA. Hao, YQ, Shanghai Jiao Tong Univ, Peoples Hosp 9, Sch Med, Dept Orthoped Surg, Shanghai 200030, Peoples R China. [hao\\_yongqiang@hotmail.com](mailto:hao_yongqiang@hotmail.com)

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## **Hematology, Medical Oncology & Josephine Ford Cancer Center**

Weinmann, S., J. A. Shapiro, B. A. Rybicki, S. M. Enger, S. K. Van Den Eeden, K. E. Richert-Boe and N. S. Weiss (2010). "Medical history, body size, and cigarette smoking in relation to fatal prostate cancer." [Cancer Causes & Control](#) **21**(1): 117-125. [PDF Full-Text](#)

[Weinmann, Sheila; Richert-Boe, Kathryn E.] Kaiser Permanente NW, Ctr Hlth Res, Portland, OR USA. [Shapiro, Jean A.] Ctr Dis Control & Prevent, Div Canc Prevent & Control, Atlanta, GA USA. [Rybicki, Benjamin A.] Henry Ford Hlth Syst, Josephine Ford Canc Ctr, Detroit, MI USA. [Enger, Shelley M.] Kaiser Permanente, Dept Res & Evaluat, Pasadena, CA USA. [Van Den Eeden, Stephen K.] Kaiser Permanente, Dept Res, Oakland, CA USA. [Weiss, Noel S.] Univ Washington, Sch Publ Hlth & Community Med, Seattle, WA 98195 USA. Weinmann, S, Kaiser Permanente NW, Ctr Hlth Res, 3800 N Interstate Ave, Portland, OR USA. [Sheila.Weinmann@kpchr.org](mailto:Sheila.Weinmann@kpchr.org)

Prostate cancer has few known risk factors. As part of a population-based case-control study conducted in four health maintenance organizations, the authors examined the associations between fatal prostate cancer and several medical and behavioral characteristics. Cases were 768 health plan members who died of prostate adenocarcinoma during the period 1997-2001. We randomly selected controls (929) from the health plan membership and matched them to cases on health plan, age, race, and pattern of health plan membership. We examined medical records to obtain information on potential risk factors during the 10 years before the date on which prostate cancer was first suspected; the same reference date was used for the matched controls. Anthropometric characteristics, as well as personal histories of benign prostatic hypertrophy, transurethral prostatectomy, cancer, diabetes, prostatitis, hypertension, and vasectomy were largely similar for cases and controls. Men who died from prostate cancer were more likely than controls to have been cigarette smokers according to the most recent smoking notation before the reference date (odds ratio 1.5, 95% confidence interval 1.1-2.0). The observed increase in risk associated with recent cigarette smoking is consistent with the findings of several other studies. However, in contrast with some reports, we observed no connection between fatal prostate cancer and some prior health conditions or measures of body size.

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## **Hypertension & Vascular Research**

Beierwaltes, W. H. (2010). "The role of calcium in the regulation of renin secretion." [Am J Physiol Renal Physiol](#) **298**(1): F1-F11. 2806121. [PDF Full-Text](#)

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Renin is the enzyme which is the rate-limiting step in the formation of the hormone angiotensin II. Therefore, the regulation of renin secretion is critical in understanding the control of the renin-angiotensin-aldosterone system and its many biological and pathological actions. Renin is synthesized, stored in, and released from the juxtaglomerular (JG) cells of the kidney. While renin secretion is positively regulated by the "second messenger" cAMP, unlike most secretory cells, renin secretion from the JG cell is inversely related to the extracellular and intracellular calcium concentrations. This novel relationship is referred to as the "calcium paradox." This review will address observations made over the past 30 years regarding calcium and the regulation of renin secretion, and focus on recent observations which address this scientific conundrum. These include 1) receptor-mediated pathways for changing intracellular calcium; 2) the discovery of a calcium-inhibitable isoform of adenylyl cyclase associated with renin in the JG cells; 3) calcium-sensing receptors in the JG cells; 4) calcium-calmodulin-mediated signals; 5) the role of phosphodiesterases; and 6) connexins, gap junctions, calcium waves, and the cortical extracellular calcium environment. While cAMP is the dominant second messenger for renin secretion, calcium appears to modulate the integrated activities of the enzymes, which balance cAMP synthesis and degradation. Thus this review concludes that calcium modifies the amplitude of cAMP-mediated renin-signaling pathways. While calcium does not directly control renin secretion, increased calcium inhibits and decreased calcium amplifies cAMP-stimulated renin secretion.

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## **Hypertension & Vascular Research**

He, Q., P. Harding and M. C. LaPointe (2010). "PKA, Rap1, ERK1/2, and p90RSK mediate PGE2 and EP4 signaling in neonatal ventricular myocytes." [Am J Physiol Heart Circ Physiol](#) **298**(1): H136-43. 2806144. [PDF Full-Text](#)

We have previously reported that 1) inhibition of cyclooxygenase-2 and PGE(2) production reduces hypertrophy after myocardial infarction in mice and 2) PGE(2) acting through its EP4 receptor causes hypertrophy of neonatal ventricular myocytes (NVMs) via ERK1/2. It is known that EP4 couples to adenylate cyclase, cAMP, and PKA. The present study was designed to determine interactions between the cAMP-PKA pathway and ERK1/2 and to further characterize events downstream of ERK1/2. We hypothesized that PKA and the small GTPase Rap are upstream of ERK1/2 and that 90-kDa ribosomal S6 kinase (p90RSK) is activated downstream. Treatment of NVMs with PGE(2) activated Rap, and this activation was inhibited in part by an EP4 antagonist and PKA inhibition. Transfection of a dominant negative mutant of Rap reduced PGE(2) activation of ERK1/2. PGE(2) activation of p90RSK was also dependent on EP4, PKA, and Rap. We also tested the involvement of Rap, ERK1/2, and p90RSK in PGE(2) regulation of gene expression. PGE(2) stimulation of brain natriuretic peptide promoter activity was blocked by either ERK1/2 inhibition or a dominant negative mutation of p90RSK. PGE(2) stimulation of c-Fos was dependent on EP4, PKA, ERK1/2, and p90RSK, whereas only the latter two kinases were involved in PGE(2) regulation of early growth response-1. Finally, we tested the involvement of EP4-dependent signaling in the NVM growth response and found that the overexpression of EP4 increased NVM cell size. We conclude that EP4-dependent signaling in NVMs in part involves PKA, Rap, ERK1/2, and p90RSK and results in the increased expression of brain natriuretic peptide and c-Fos.

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### **Hypertension & Vascular Research**

Hong, N. J., G. B. Silva and J. L. Garvin (2010). "PKCalpha mediates flow-stimulated superoxide production in thick ascending limbs." [Am J Physiol Renal Physiol](#) **EPub Ahead of Print**. [PDF Full-Text](#)

Henry Ford Hospital.

We have shown that luminal flow increases net superoxide (O<sub>2</sub><sup>-</sup>) production via NADPH oxidase in thick ascending limbs. Protein kinase C (PKC) activates NADPH oxidase activity in phagocytes, cardiomyocytes, aortic endothelial cells, vascular smooth muscle cells, and renal mesangial cells. However, the flow-activated pathway that induces NADPH oxidase activity in thick ascending limbs is unclear. We hypothesized that PKC mediates flow-stimulated net O<sub>2</sub><sup>-</sup> production by thick ascending limbs. Initiation of flow (20 nl/min) increased net O<sub>2</sub><sup>-</sup> production from 4 +/- 1 to 61 +/- 12 AU/s (p < 0.007; n = 5). The NADPH oxidase inhibitor apocynin completely blocked the flow-induced increase in net O<sub>2</sub><sup>-</sup> production (2 +/- 1 vs. 1 +/- 1 AU/s; p > 0.05; n = 5). Flow-stimulated O<sub>2</sub><sup>-</sup> was also blocked in p47(phox)-deficient mice. We measured flow-stimulated PKC activity with a fluorescence resonance energy transfer (FRET)-based membrane-targeted PKC activity reporter and found that the FRET ratio increased from 0.87 +/- 0.02 to 0.96 +/- 0.04 AU (p < 0.05; n = 6). In the absence of flow, the PKC activator phorbol 12-myristate 13-acetate (PMA; 200nM) enhanced net O<sub>2</sub><sup>-</sup> production from 5 +/- 2 to 92 +/- 6 AU/s (p < 0.001; n = 6). The PKCalpha- and beta-selective inhibitor Go 6976 (100 nM) decreased flow-stimulated net O<sub>2</sub><sup>-</sup> production from 54 +/- 15 to 2 +/- 1 AU/s (p < 0.04; n = 5). Flow-induced net O<sub>2</sub><sup>-</sup> production was inhibited in thick ascending limbs transduced with dominant-negative (dn)PKCalpha but not dnPKCbeta or LacZ (Delta = 11 +/- 3 AU/s for dnPKCalpha; 55 +/- 7 AU/s for dnPKCbeta and 63 +/- 7 AU/s for LacZ; p < 0.001; n = 6). We concluded that flow stimulates net O<sub>2</sub><sup>-</sup> production in thick ascending limbs via PKCalpha-mediated activation of NADPH oxidase. Key words: Reactive oxygen species, protein kinases, NADPH oxidase, luminal flow.

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### **Infectious Diseases**

Nagappan, V., D. Boikov and J. A. Vazquez (2010). "Assessment of the In Vitro Kinetic Activity of Caspofungin against *Candida glabrata*." [Antimicrobial Agents and Chemotherapy](#) **54(1)**: 522-525. [PDF Full-Text](#)

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Echinocandins have become the drug of choice in infections caused by *Candida glabrata*. The objective of this study was to evaluate the in vitro activity of caspofungin alone and in combination against *C. glabrata*. In vitro assays demonstrated that caspofungin alone showed excellent fungicidal activity against *C. glabrata*, including fluconazole-resistant strains. The combination of caspofungin and azole antifungals showed potential synergy against *C. glabrata*. Overall, caspofungin demonstrated excellent in vitro activity, alone and in combination, against strains of *C. glabrata*.

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## Infectious Diseases

Osawa, R., B. D. Alexander, O. Lortholary, F. Dromer, G. N. Forrest, G. M. Lyon, J. Somani, K. L. Gupta, R. del Busto, T. L. Pruett, C. D. Sifri, A. P. Limaye, G. T. John, G. B. Klintmalm, K. Pursell, V. Stosor, M. I. Morris, L. A. Dowdy, P. Munoz, A. C. Kalil, J. Garcia-Diaz, S. Orloff, A. A. House, S. Houston, D. Wray, S. Huprikar, L. B. Johnson, A. Humar, R. R. Razonable, R. A. Fisher, S. Husain, M. M. Wagener and N. Singh (2010). "Identifying Predictors of Central Nervous System Disease in Solid Organ Transplant Recipients With Cryptococcosis." *Transplantation* **89**(1): 69-74. [PDF Full-Text](#)

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**Background.** Cerebrospinal fluid (CSF) analysis is often deferred in patients with cryptococcal disease, particularly in the absence of neurologic manifestations. We sought to determine whether a subset of solid organ transplant (SOT) recipients with high likelihood of central nervous system (CNS) disease could be identified in whom CSF analysis must be performed. **Methods.** Patients comprised a multicenter cohort of SOT recipients with cryptococcosis. **Results.** Of 129 (88%) of 146 SOT recipients with cryptococcosis who underwent CSF analysis, 80 (62%) had CNS disease. In the overall study population, abnormal mental status, time to onset of cryptococcosis more than 24 months posttransplantation (late-onset disease), serum cryptococcal antigen titer more than 1:64, and fungemia were independently associated with an increased risk of CNS disease. Of patients with abnormal mental status, 95% had CNS cryptococcosis. When only patients with normal mental status were considered, three predictors (serum antigen titer >1:64, fungemia, and late-onset disease) independently identified patients with CNS cryptococcosis; the risk of CNS disease was 14% if none, 39% if one, and 94% if two of the aforementioned predictors existed (chi(2) for trend P<0.001). **Conclusions.** CSF analysis should be strongly considered in SOT recipients with cryptococcosis who have late-onset disease, fungemia, or serum cryptococcal antigen titer more than 1:64 even in the presence of normal mental status.

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## Internal Medicine

Habib, Z. A., S. L. Havstad, K. Wells, G. Divine, M. Pladevall and L. K. Williams (2010). "Thiazolidinedione Use and the Longitudinal Risk of Fractures in Patients with Type 2 Diabetes Mellitus." J Clin Endocrinol Metab **EPub Ahead of Print**. [PDF Full-Text](#)

Departments of Internal Medicine (Z.A.H., L.K.W.) and Biostatistics and Research Epidemiology (S.L.H., K.W., G.D., L.K.W.), and Center for Health Services Research (M.P., L.K.W.), Henry Ford Hospital, Detroit, Michigan 48202.

Context: Thiazolidinedione (TZD) use has recently been associated with an increased risk of fractures. Objective: The aim of this study was to determine the time-dependent relationship between TZD use and fracture risk. Design: We conducted a retrospective cohort study in a large health system in southeast Michigan. Patients: Patients who received care from the health system were included if they were at least 18 yr of age, had a diagnosis of diabetes, and had at least one prescription for an oral diabetes medication. These criteria identified 19,070 individuals (9,620 women and 9,450 men). Intervention: This study compared patients treated with TZDs to patients without TZD treatment. Cox proportional hazard models were used to assess the relationship between exposure and outcomes. Main Outcome Measures: The primary outcome was the time to fracture. Secondary analyses examined the risk of fractures in subgroups defined by sex and age. Results: TZD use was associated with an increased risk of fracture in the cohort overall [adjusted hazard ratio (aHR), 1.35; 95% confidence interval (CI), 1.05-1.71] and in women (aHR, 1.57; 95% CI, 1.16-2.14), but not in men (aHR, 1.05; 95% CI, 0.70-1.58). Women more than 65 yr of age appeared to be at greatest risk for fracture (aHR, 1.72; 95% CI, 1.17-2.52). Among women, the increased fracture risk was not apparent until after 1 yr of TZD treatment. Conclusions: TZD use was associated with an increased risk for fractures in women, particularly at ages above 65 yr. Clinicians should be aware of this association when considering TZD therapy so as to appropriately manage and counsel their patients.

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### **Internal Medicine**

Kim, Y. K., R. Nieuwlaat, S. J. Connolly, S. Schulman, K. Meijer, N. Raju, S. Kaatz and J. W. Eikelboom (2010). "Effect of a simple two-step warfarin dosing algorithm on anticoagulant control as measured by time in therapeutic range: a pilot study." Journal of Thrombosis and Haemostasis **8**(1): 101-106. [PDF Full-Text](#)

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Background: The efficacy and safety of vitamin K antagonists for the prevention of thromboembolism are dependent on the time for which the International Normalized Ratio (INR) is in the therapeutic range. The objective of our study was to determine the effect of introducing a simple two-step dosing algorithm, as compared with dosing by anticoagulation clinic staffs on the basis of their experience, on time in therapeutic range (TTR) of warfarin therapy. Methods: We compared TTRs of all clinic patients before and after the introduction of a simple two-step dosing algorithm at a single anticoagulation clinic in Canada, between 1 August 2006 and 24 December 2008. TTR was calculated using the linear interpolation method of Rosendaal. Results: We included 873 patients in the 'before' phase and 1088 patients in the 'after' phase. Introduction of the dosing algorithm significantly increased TTR of patients with a therapeutic INR range of 2-3 from 67.2% to 73.2% ( $P < 0.001$ ), and that of patients with a therapeutic INR range of 2.5-3.5 from 49.8% to 63.8% ( $P < 0.001$ ). Conclusions: The introduction of a simple two-step warfarin-dosing algorithm in place of dosing by experienced anticoagulation clinic staff significantly improved mean TTR for patients in a tertiary-care anticoagulation clinic. This inexpensive and widely applicable algorithm has the potential to improve warfarin control.

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### **Nephrology**

Novak, J. E. and L. A. Szczech (2010). "HIV through a nephrologist's lens." Adv Chronic Kidney Dis **17**(1): 3-4. [PDF Full-Text](#)

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## Nephrology

Szamosfalvi, B., S. Frinak and J. Yee (2010). "Automated regional citrate anticoagulation: technological barriers and possible solutions." *Blood Purif* **29**(2): 204-9. [PDF Full-Text](#)

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**BACKGROUND:** Large-scale adoption of regional citrate anticoagulation (RCA) is prevented by risks of the technique as practiced traditionally. Safe RCA protocols with automated delivery on customized dialysis systems are needed. **METHODS:** We applied kinetic analysis of solute fluxes during RCA to design a protocol for sustained low-efficiency dialysis (SLED) for critically ill patients. We used a high-flux hemodialyzer, a zero-calcium (Ca) dialysate, a dialysis machine with online clearance and access recirculation monitoring, and a separate optical hematocrit (Hct) sensor. Flow rates were Q(B) = 200 ml/min for blood; Q(D) = 400 ml/min for dialysate, with Na = 140 mmol/l and HCO(3) = 32 mmol/l; Q(citrate) = 400 ml/h of acid citrate dextrose A; ultrafiltration as indicated. The Q(Ca) was infused into the return blood line, adjusted hourly based on online Hct and a <24-hour-old albumin level. **RESULTS:** Using the SLED-RCA protocol in an hepatic, ex vivo dialysis system, ionized Ca (iCa) was >1 mmol/l in the blood reservoir and <0.3 mmol/l in the blood circuit after citrate but before Ca infusion (Q(Ca)) with normal electrolyte composition of the blood returning to the reservoir. Clinically, SLED-RCA completely abrogated clotting, without adverse electrolyte effects. The Q(Ca) prediction algorithm maintained normal systemic iCa (0.95-1.4 mmol/l) in all patients. The high citrate extraction on the dialyzer prevented systemic citrate accumulation even in shock liver patients. Safety analysis shows that building a dialysis system for automated SLED-RCA is feasible. **CONCLUSION:** Using predictive Q(Ca) dosing and integrating control of the infusion pumps with the dialysis machine, SLED-RCA can be near-automated today to provide a user-friendly and safe system.

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## Neurology

Chen, J. L., A. Zacharek, X. Cui, A. Shehadah, H. Jiang, C. Roberts, M. Lu and M. Chopp (2010). "Treatment of stroke with a synthetic liver X receptor agonist, TO901317, promotes synaptic plasticity and axonal regeneration in mice." *Journal of Cerebral Blood Flow and Metabolism* **30**(1): 102-109. [PDF Full-Text](#)

[Chen, Jieli; Zacharek, Alex; Cui, Xu; Shehadah, Amjad; Jiang, Hao; Roberts, Cynthia; 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. Chen, JL, Henry Ford Hosp, Dept Neurol, E&R Bldg, Room 3091, 2799 W Grand Blvd, Detroit, MI 48202 USA. [jieli@neuro.hfh.edu](mailto:jieli@neuro.hfh.edu)

In this study, we tested the hypothesis that TO901317 promotes synapse plasticity and axonal regeneration after stroke. Adult male C57BL/6J mice were subjected to middle cerebral artery occlusion (MCAo) and treated with or without TO901317 starting 24 h after MCAo daily for 14 days. Axonal damage and regeneration were evaluated by immunostaining. TO901317 significantly increased synaptophysin expression and axonal regeneration, as well as decreased the expressions of amyloid betaA4 precursor protein and Nogo receptor (NgR) in the ischemic brain. To test whether TO901317 regulates the phosphorylation of phosphatidylinositol 3-kinase (p-PI3K) and Akt (p-Akt) activity in the ischemic brain, MCAo mice were treated with or without TO901317 starting 24 h after MCAo daily for 4 days and were then killed at 5 days after MCAo. TO901317 treatment significantly increased p-PI3K and p-Akt activity, but did not increase total PI3K expression in the ischemic brain. Using primary cortical neuron (PCN) culture, TO901317 significantly increased synaptophysin expression, p-PI3K activity, and decreased NgR expression compared with nontreated controls. TO901317 also significantly increased neurite outgrowth, and inhibition of the PI3K/Akt pathway by LY294002 decreased neurite outgrowth in both controls and TO901317-treated groups in cultured hypoxic PCN. These data indicate that TO901317 promotes synaptic plasticity and axonal regeneration, and that PI3K/Akt signaling activity contributes to neurite outgrowth. *Journal of Cerebral Blood Flow & Metabolism* (2010) 30, 102-109; doi: 10.1038/jcbfm.2009.187; published online 2 September 2009

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## Neurology

Jiang, H., X. Shang, H. T. Wu, G. Huang, Y. Y. Wang, S. Al-Holou, S. C. Gautam and M. Chopp (2010). "Combination Treatment with Resveratrol and Sulforaphane Induces Apoptosis in Human U251 Glioma Cells." Neurochemical Research **35**(1): 152-161. [PDF Full-Text](#)

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Resveratrol is a naturally occurring polyphenolic compound highly enriched in grapes, peanuts, red wine, and a variety of food sources. Sulforaphane belongs to the family of isothiocyanates and is highly enriched in cruciferous vegetables. Our previous study showed that resveratrol, when used at high concentrations, inhibited cell proliferation, caused the cell cycle arrest and induced apoptotic cell death in glioma cells. In the current study, we tested the effect of combination treatment with resveratrol and sulforaphane, when both were used at low concentrations, on cell proliferation, migration and death in human U251 glioma cells. Our study shows that combination treatment with resveratrol and sulforaphane inhibits cell proliferation and migration, reduces cell viability, induces lactate dehydrogenase release, decreases pro-survival Akt phosphorylation and increases caspase-3 activation. The use of combination of bioactive food components, such as resveratrol and sulforaphane, may be a viable approach for the treatment of glioma.

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## Neurology

Raji, C. A., C. Lee, O. L. Lopez, J. Tsay, J. F. Boardman, E. D. Schwartz, W. S. Bartynski, H. M. Hefzy, H. M. Gach, W. Dai and J. T. Becker (2010). "Initial Experience in Using Continuous Arterial Spin-Labeled MR Imaging for Early Detection of Alzheimer Disease." AJNR Am J Neuroradiol **EPub Ahead of Print**. [PDF Full-Text](#)

Departments of Pathology, Radiology, Neurology, Psychiatry, and Psychology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Department of Radiology, University of Cincinnati Hospital, Cincinnati, Ohio; Department of Neurology, Henry Ford Hospital, Detroit, Michigan; Shields Health Care Group, Brockton, Massachusetts; Nevada Cancer Institute, University of Nevada, Las Vegas, Nevada; University of Nevada School of Medicine, Reno, Nevada; and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

**BACKGROUND AND PURPOSE:** MR imaging of the brain has significant potential in the early detection of neurodegenerative disorders such as AD. The purpose of this work was to determine if perfusion MR imaging can be used to separate AD from normal cognition in individual subjects. We investigated the diagnostic utility of perfusion MR imaging for early detection of AD compared with structural imaging. **MATERIALS AND METHODS:** Data were analyzed from 32 participants in the institutional review board-approved CHS-CS: 19 cognitively healthy individuals and 13 with clinically adjudicated AD. All subjects underwent structural T1-weighted SGPR and CASL MR imaging. Four readers with varying experience separately rated each CASL and SPGR scan finding as normal or abnormal on the basis of standardized qualitative diagnostic criteria for observed perfusion abnormalities on CASL or volume loss on SPGR and rated the confidence in their evaluation. **RESULTS:** Inter-rater reliability was superior in CASL ( $\kappa = 0.7$  in experienced readers) compared with SPGR ( $\kappa = 0.17$ ). CASL MR imaging had the highest sensitivity (85%) and accuracy (70%). Frontal lobe CASL findings increased sensitivity to 88% and accuracy to 79%. Fifty-seven percent of false-positive readings with CASL were in controls with cognitive decline or instability within 5 years. Three of the 4 readers revealed a statistically significant relationship between confidence and correct classification when using CASL. **CONCLUSIONS:** Readers were able to separate individuals with mild AD from those with normal cognition with high sensitivity by using CASL but not volumetric MR imaging. This initial experience suggests that CASL MR imaging may be a useful technique for detecting AD.

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## Neurology

Santra, M., X. G. Zheng, C. Roberts, S. Santra, M. Lu, S. Panda, F. Jiang and M. Chopp (2010). "Single Doublecortin Gene Therapy Significantly Reduces Glioma Tumor Volume." Journal of Neuroscience Research **88**(2): 304-314. [Article Request Form](#)

[Santra, Manoranjan; Zheng, Xuguang; Roberts, Cindi; Santra, Sutapa; Lu, Mei; Panda, Swayamprava; Jiang, Feng; Chopp, Michael] Henry Ford Hosp, Dept Neurol, Detroit, MI 48202 USA. [Chopp, Michael] Oakland Univ, Dept Phys, Rochester, MI USA. Chopp, M, Henry Ford Hosp, Dept Neurol, Educ & Res Bldg, Room 3056, 2799 W Grand Blvd, Detroit, MI 48202 USA. [chopp@neuro.hfh.edu](mailto:chopp@neuro.hfh.edu)

We employed lentivirus-based doublecortin (DCX), as a glioma suppressor gene therapy in an intracranial glioma tumor xenograft model in nude rats. Single DCX-expressing lentivirus was directly administered into the tumor on day 8 after U87 tumor cell implantation. DCX treatment significantly reduced U87 glioma tumor volume (similar to 60%) on day 14 after DCX lentivirus injection and significantly improved median survival of tumor-bearing nude rats. DCX synthesis induced neuronal markers MAP2, TUJ1, and PSA-NCAM and the glial marker glial fibrillary acidic protein (GFAP) in the implanted U87 glioma tumors. DCX synthesis induced GFAP that colocalized with tubulin in the mitotic stage, inhibited cleavage furrow during cytokinesis, and blocked mitosis in glioma cells. DCX lentivirus infection did not induce apoptosis but significantly inhibited expression of the proliferation marker Ki-67 and the blood vessel marker von-Willebrand factor (vWF). U87 and other glioma cells except for brain tumor stem cells (BTSCs) do not express neuronal markers or both neuronal and glial markers. DCX-synthesizing glioma cells express a phenotype of antiangiogenic BTSC-like cells with terminal differentiation that causes remission of glioma cells by blocking mitosis via a novel DCX/GFAP pathway. Direct local delivery of lentivirus-based DCX gene therapy is a potential differentiation-based therapeutic approach for the treatment of glioma. (C) 2009 Wiley-Liss, Inc.

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## Neurology

Xu, P., S. Z. Yu, R. C. Jiang, C. S. Kang, G. X. Wang, H. Jiang and P. Y. Pu (2009). "Differential Expression of Notch Family Members in Astrocytomas and Medulloblastomas." Pathology & Oncology Research **15**(4): 703-710. [PDF Full-Text](#)

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Notch signaling pathway plays an integral role in determining cell fates in development. Growing evidence demonstrates that Notch signaling pathway has versatile effects in tumorigenesis depending on the tumor type, grade and stage. Notch signaling pathway is deregulated in some brain tumors. To examine the differential expression of Notch family members (Notch1, 2, 3, 4) in human astrocytomas and medulloblastomas, and to evaluate their roles in the development of both tumor types. Immunohistochemical staining and Western blot analysis were used to detect Notch1, 2, 3, 4 expression in tissue microarray and freshly resected tissue samples of normal brain, astrocytomas and medulloblastomas. Notch family members were not expressed or barely detectable in normal brain tissues. Notch1, 3, 4 were highly expressed but Notch2 was not expressed in astrocytomas. The percentage of immunopositive tumor cells and level of Notch1 expression was increased with tumor grade. In addition, overexpression of Notch2 was detected in medulloblastomas in contrast to low or no expression of Notch1, 3, 4. Differential expression of Notch1, 2, 3, 4 is detected in astrocytomas and medulloblastomas, that may be related to their different roles playing in the development of brain tumors.

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## Neurology

Zacharek, A., A. Shehadah, J. 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 **EPub Ahead of Print**. [PDF Full-Text](#)

From the Departments of Neurology and Biostatistics and Research Epidemiology, Henry Ford Health Sciences Center, Detroit, Mich; and the Department of Physics, Oakland University, Rochester, Mich.

**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 Flk1 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.

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## Neurosurgery

Signorelli, F., J. Guyotat, K. Elisevich and G. M. V. Barbagallo (2010). "Review of current microsurgical management of insular gliomas." *Acta Neurochirurgica* **152**(1): 19-26. [PDF Full-Text](#)

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The insular lobe is a functionally complex structure, harbouring peculiar anatomical and vascular features and specific neuronal connectivity with surrounding cerebral structures. It is situated in the depth of the Sylvian fissure and can be affected by either low-grade or high-grade gliomas. Because of its complexity, surgery of insular tumours has been traditionally regarded as hazardous. Nonetheless, currently improved diagnostic, neurophysiological and surgical tools allow the neurosurgeon to perform surgery of insular gliomas in a safer way, thus bringing forward the pioneering work performed by neurosurgeons in the past two decades. The aim of this paper is to provide the reader with an updated review of the anatomy, the clinical picture, diagnosis and surgical management of insular gliomas.

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## Obstetrics & Gynecology

Brenot, K. and G. L. Goyert (2009). "Impact of Robotic Surgery on Obstetric-Gynecologic Resident Training." *Journal of Reproductive Medicine* **54**(11-12): 675-677. [Article Request Form](#)

[Brenot, Karen; Goyert, Gregory L.] Henry Ford Wyandotte Hosp, Dept Obstet & Gynecol, Wyandotte, MI USA. Goyert, GL, 2275 W Jefferson, Trenton, MI 48183 USA. [gregorygi@aol.com](mailto:gregorygi@aol.com)

**OBJECTIVE:** To compare the volume and type of surgical techniques for hysterectomies performed prior to and after the introduction of robotic surgery at our institution and to assess the potential impact on obstetric-gynecologic resident training. **STUDY DESIGN:** A retrospective study examined the number and types of hysterectomies performed at our institution during the 18 months prior to, and the 18 months after, the introduction of a robotic surgical system. Procedures performed during both time periods were compared by number and percentage using the chi(2) or Fisher's exact test for counts, <5. **RESULTS:** A total of 903 hysterectomies were performed from July 1, 2005, to July 1, 2008. There were 444 hysterectomies in the prerobotic surgical system group and 459 hysterectomies in the postrobotic surgical system group. There was a statistically significant decrease in the number of laparoscopically assisted vaginal hysterectomies (94 vs. 36;  $p < 0.001$ ) and total abdominal hysterectomies (249 vs. 203;  $p < 0.001$ ) performed. **CONCLUSION:** This study demonstrated a significant impact on the volume and type of surgical techniques for hysterectomies performed prior to and after the introduction of robotic surgery at our institution. This observation may have direct consequences for obstetric-gynecologic resident surgical experience. (*J Reprod Med* 2009;54:675-677)

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## Otolaryngology

Schweitzer, V. G. and M. L. Somers (2010). "PHOTOFRIN-mediated photodynamic therapy for treatment of early stage (Tis-T2N0M0) SqCCA of oral cavity and oropharynx." Lasers Surg Med **42**(1): 1-8. [Article Request Form](#)

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**OBJECTIVES:** To evaluate the efficacy of dihematoporphyrin ether (PHOTOFRIN)-mediated photodynamic therapy (PDT) for the treatment of diffuse field cancerization and Tis-T2N0M0 squamous cell carcinoma (SqCCA) of the oral cavity and oropharynx in patients not amenable to or that have failed conventional head and neck cancer treatment. **METHODS:** This is a retrospective study of 30 patients with Tis-T2N0M0 SqCCA of the oral cavity/oropharynx treated with PDT. Intravenous PHOTOFRIN (porfimer sodium) (dose 2.0 mg/kg) was administered outpatient, followed 48-60 hours later by intraoperative photoactivation at 630 nm via fiberoptic microlens surface delivery (light dose 50-100 J/cm(2)) or interstitial implantation via cylindrical diffuser fiberoptic delivery (light dose 50-100 J/cm). **RESULTS:** Twenty-four of 30 patients (80%) have demonstrated complete remission (follow-up 3-144 months). There were six patients who had partial remission with recurrence observed at 3, 3, 5, 9, 23, and 26 months subsequently retreated with conventional therapy. Eleven of 24 patients were cancer disease free at 2 years following PDT. **CONCLUSION:** PDT provides a surgical oncologic modality for potentially curative treatment of early stage oral cavity and oropharyngeal malignancies either as a primary modality or for treatment in patients that have previously failed surgery and/or radiation therapy.

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## Pathology

Fagerlin, A., B. J. Zikmund-Fisher, D. M. Smith, V. Nair, H. A. Derry, J. B. McClure, S. Greene, A. Stark, S. H. Alford, P. Lantz, D. F. Hayes, C. Wiese, S. C. Zweig, R. Pitsch, A. Jankovic and P. A. Ubel (2010). "Women's decisions regarding tamoxifen for breast cancer prevention: responses to a tailored decision aid." Breast Cancer Research and Treatment **119**(3): 613-620. [PDF Full-Text](#)

[Fagerlin, Angela; Zikmund-Fisher, Brian J.; Smith, Dylan M.; Derry, Holly A.; Pitsch, Rosemarie; Jankovic, Aleksandra; Ubel, Peter A.] Ctr Behav & Decis Sci Med, Ann Arbor, MI 48109 USA. [Fagerlin, Angela; Zikmund-Fisher, Brian J.; Smith, Dylan M.; Ubel, Peter A.] Ctr Clin Management Res, Ann Arbor VA HSR&D, Ann Arbor, MI USA. [Fagerlin, Angela; Zikmund-Fisher, Brian J.; Smith, Dylan M.; Ubel, Peter A.] Univ Michigan, Div Gen Internal Med, Ann Arbor, MI 48109 USA. [Nair, Vijayan] Univ Michigan, Dept Stat, Ann Arbor, MI 48109 USA. [McClure, Jennifer B.; Greene, Sarah; Wiese, Cheryl] Grp Hlth Ctr Hlth Studies, Seattle, WA USA. [Stark, Azadeh; Alford, Sharon Hensley; Zweig, Sarah Claud] Henry Ford Hlth Syst, Detroit, MI USA. [Lantz, Paula] Univ Michigan, Sch Publ Hlth, Ann Arbor, MI 48109 USA. [Hayes, Daniel F.] Univ Michigan, Breast Oncol Program, Ctr Comprehens Canc, Ann Arbor, MI 48109 USA. [Ubel, Peter A.] Univ Michigan, Dept Psychol, Ann Arbor, MI 48109 USA. Fagerlin, A, Ctr Behav & Decis Sci Med, 300 N Ingalls, Rm 7C27, Ann Arbor, MI 48109 USA. [fagerlin@umich.edu](mailto:fagerlin@umich.edu)

Tamoxifen reduces primary breast cancer incidence, yet causes serious side effects. To date, few women with increased breast cancer risk have elected to use tamoxifen for chemoprevention. The objective of the study was to determine women's knowledge of and attitudes toward tamoxifen following exposure to a tailored decision aid (DA). A total of 632 women with a 5-year risk of breast cancer a parts per thousand yen 1.66% (Mean = 2.56, range = 1.7-17.3) were recruited from two healthcare organizations. Participants viewed an online DA that informed them about their 5-year risk of breast cancer and presented individually tailored content depicting the risks/benefits of tamoxifen prophylaxis. Outcome measures included behavioral intentions (to seek additional information about tamoxifen, to talk to a physician about tamoxifen, and to take tamoxifen); knowledge; and perceived risks and benefits of tamoxifen. After viewing the DA, 29% of participants said they intended to seek more information or talk to their doctor about tamoxifen, and only 6% believed they would take tamoxifen. Knowledge was considerable, with 63% of women answering at least 5 of 6 knowledge questions correctly. Participants were concerned about the risks of tamoxifen, and many believed that the benefits of tamoxifen did not outweigh the risks. This study is the largest to date to test women's preferences for taking tamoxifen and one of the largest to have tested the impact of a tailored DA. After

viewing the DA, women demonstrated good understanding of tamoxifen's risks and benefits, but most were not interested in taking tamoxifen for breast cancer chemoprevention.

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## Pathology

Mammen, J. J. and J. M. Tuthill (2008). "Structuring data in pathology reports: overcoming challenges with new tools." AMIA Annu Symp Proc: 1041. [Article Request Form](#)

Henry Ford Hospital, Detroit, MI, USA.

Traditional pathology reports have been textual with a high degree of variability. Checklist based structured pathology reports contribute significantly towards standardization and error reduction. As implemented, most of these are text templates making data retrieval dependent on natural language search. We describe a toolset that has been used to construct Laboratory Information System (LIS)-integrated checklists with forward chaining inference capabilities and contextual decision support. Data is saved directly into the LIS database facilitating queries and reporting.

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## Pharmacy

Adams, J., N. Patel, N. Mankaryous, M. Tadros and C. D. Miller (2010). "Nonnucleoside Reverse Transcriptase Inhibitor Resistance and the Role of the Second-Generation Agents." Annals of Pharmacotherapy **44**(1): 157-165. [PDF Full-Text](#)

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**OBJECTIVE:** To review the current state of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance, discuss the promising role of second-generation NNRTIs, and provide insight into their clinical utility. **DATA SOURCES:** Articles were identified through searches of MEDLINE (May 2000-August 2009) and International Pharmaceutical Abstracts (May 1998-August 2009), using the key words etravirine, rilpivirine, TMC125, TMC278, diarylpyrimidine, NNRTI, and resistance. **STUDY SELECTION AND DATA EXTRACTION:** Clinical trials, resistance studies, and pharmacokinetic data were selected for review. **DATA SYNTHESIS:** NNRTIs are an integral class of antiretroviral agents utilized for the treatment of HIV-1 infection. These agents have become preferred therapy options for treatment-naive individuals per treatment guideline recommendations and have gained increased popularity over protease inhibitor-based antiretroviral therapy. However, available NNRTIs possess inherent characteristics, such as low genetic barrier to resistance and high degree of cross-resistance, that limit their use in HIV therapy. Due to the growing utilization of this highly efficacious antiretroviral class and the increased capability for resistance development, many HIV-infected patients have experienced treatment failure of an NNRTI. Cross-resistance makes other first-generation NNRTI agents unavailable for future use. Etravirine and rilpivirine are second-generation NNRTIs that are not significantly hampered by cross-resistance and possess potent antiretroviral activity against current NNRTI-resistant viral strains. These agents provide new and important therapy options for many HIV-infected patients. **CONCLUSIONS:** NNRTI resistance is an increasing problem that may impair the chances for therapeutic success in HIV-infected patients. Novel agents such as etravirine and rilpivirine provide new, sensitive options for patients and significantly improve the rate of virologic suppression when appropriately applied. **KEY WORDS:** diarylpyrimidine, etravirine, HIV, NNRTI, resistance, rilpivirine.

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## Pharmacy

Jennings, D. L. and J. S. Kalus (2010). "Addition of Cilostazol to Aspirin and a Thienopyridine for Prevention of Restenosis After Coronary Artery Stenting: A Meta-Analysis." J Clin Pharmacol **EPub Ahead of Print**. [PDF Full-Text](#)

Henry Ford Hospital.

The purpose of this study is to evaluate the effect of adding cilostazol to dual antiplatelet therapy (aspirin and thienopyridine) on rates of restenosis after coronary artery stenting. A meta-analysis is conducted of randomized, controlled trials comparing 3 drug regimens (cilostazol, thienopyridine, aspirin [triple therapy]) with dual anti-platelet therapy to reduce restenosis after coronary stenting. A total of 5 studies are included for analysis. The analysis reveals that triple therapy is used in 796 patients, whereas dual therapy is used in 801 patients. Approximately 56% of patients receive a drug-eluting stent. The 6-month restenosis rates are significantly lower with triple versus dual antiplatelet therapy (12.7% vs 21.9%; odds ratio 0.5; 95% confidence interval, 0.38-0.66;  $P < .001$ ). This benefit is seen regardless of whether a bare-metal or drug-eluting stent is used. Rates of major adverse cardiac events and bleeding are reported for 3 of the 5 studies ( $n = 1426$ ); analysis of these outcomes shows no difference between treatment groups ( $P = .21$  and  $.48$ , respectively). The addition of cilostazol to standard dual antiplatelet therapy reduces angiographic restenosis and increases MLD at 6 months without significantly affecting rates of major adverse cardiac events or bleeding.

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## **Pulmonary & Critical Care Medicine**

Adriole, G. L., C. ED, r. Grubb RL, S. Buys, D. Chia, T. Church, M. Fouad, E. Gelmann, P. Kvale, D. Reding, J. Weissfeld, L. Yokochi, B. O'Brien, J. Clapp, J. Rathmell, T. Riley, R. Hayes, B. Kramer, G. Izmirlian, A. Miller, P. Pinsky, P. Prorok, J. Gohagan, C. Berg and PLCO Project Team (2009). "Mortality results from a randomized prostate-cancer screening trial." [N Engl J Med](#) **360**(13): 1310-9. [PDF Full-Text](#)

Henry Ford Hospital, Pulmonary & Critical Care Medicine, Detroit, MI

**BACKGROUND:** The effect of screening with prostate-specific-antigen (PSA) testing and digital rectal examination on the rate of death from prostate cancer is unknown. This is the first report from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial on prostate-cancer mortality. **METHODS:** From 1993 through 2001, we randomly assigned 76,693 men at 10 U.S. study centers to receive either annual screening (38,343 subjects) or usual care as the control (38,350 subjects). Men in the screening group were offered annual PSA testing for 6 years and digital rectal examination for 4 years. The subjects and health care providers received the results and decided on the type of follow-up evaluation. Usual care sometimes included screening, as some organizations have recommended. The numbers of all cancers and deaths and causes of death were ascertained. **RESULTS:** In the screening group, rates of compliance were 85% for PSA testing and 86% for digital rectal examination. Rates of screening in the control group increased from 40% in the first year to 52% in the sixth year for PSA testing and ranged from 41 to 46% for digital rectal examination. After 7 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2820 cancers) in the screening group and 95 (2322 cancers) in the control group (rate ratio, 1.22; 95% confidence interval [CI], 1.16 to 1.29). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI, 0.75 to 1.70). The data at 10 years were 67% complete and consistent with these overall findings. **CONCLUSIONS:** After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups. (ClinicalTrials.gov number, NCT00002540.)

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## **Pulmonary & Critical Care Medicine**

Castro, M., A. S. Rubin, M. Laviolette, J. Fiterman, M. D. Lima, P. L. Shah, E. Fiss, R. Olivenstein, N. C. Thomson, R. M. Niven, I. D. Pavord, M. Simoff, D. R. Duhamel, C. McEvoy, R. Barbers, N. H. T. ten Hacken, M. E. Wechsler, M. Holmes, M. J. Phillips, S. Erzurum, W. Lunn, E. Israel, N. Jariour, M. Kraft, N. S. Shargill, J. Quiring, S. M. Berry and G. Cox (2010). "Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma A Multicenter, Randomized, Double-Blind, Sham-Controlled Clinical Trial." [American Journal of Respiratory and Critical Care Medicine](#) **181**(2): 116-124. [PDF Full-Text](#)

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Rationale Bronchial thermoplasty (BT) is a bronchoscopic procedure in which controlled thermal energy is applied to the airway wall to decrease smooth muscle. Objectives: To evaluate the effectiveness and safety of BT versus a sham procedure in subjects with severe asthma who remain symptomatic despite treatment with high-dose inhaled corticosteroids and long-acting beta(2)-agonists. Methods: A total of 288 adult subjects (Intent-to-Treat [ITT]) randomized to BT or sham control underwent three bronchoscopy procedures. Primary outcome was the difference in Asthma Quality of Life Questionnaire (AQLQ) scores from baseline to average of 6, 9, and 12 months (integrated AQLQ). Adverse events and health care use were collected to assess safety. Statistical design and analysis of the primary endpoint was Bayesian. Target posterior probability of superiority (PPS) of BT over sham was 95%, except for the primary endpoint (96.4%). Measurements and Main Results: The improvement from baseline in the integrated AQLQ score was superior in the BT group compared with sham (BT, 1.35 +/- 1.10; sham, 1.16 +/- 1.23 [PPS, 96.0% ITT and 97.9% per Protocol]). Seventy-nine percent of BT and 64% of sham subjects achieved changes in AQLQ of 0.5 or greater (PPS, 99.6%). Six percent more BT subjects were hospitalized in the treatment period (up to 6 wk after BT). In the posttreatment period (6-52 wk after BT), the BT group experienced fewer severe exacerbations, emergency department (ED) visits, and days missed from work/school compared with the sham group (PPS, 95.5, 99.9, and 99.3%, respectively). Conclusions: BT in subjects with severe asthma improves asthma-specific quality of life with a reduction in severe exacerbations and healthcare use in the posttreatment period.

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## **Pulmonary & Critical Care Medicine**

Kavathia, D., J. D. Buckley, D. Rao, B. Rybicki and R. Burke (2010). "Elevated 1, 25-dihydroxyvitamin D levels are associated with protracted treatment in sarcoidosis." *Respir Med* **EPub Ahead of Print**. [PDF Full-Text](#)

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BACKGROUND: Active vitamin D metabolite, 1, 25-dihydroxyvitamin D, has pleomorphic effects on both innate and acquired immunity. Sarcoid granuloma derived 1, 25-dihydroxyvitamin D leads to hypercalcemia, but the association of 1, 25-dihydroxyvitamin D with the clinical phenotype of the disease is currently unknown. OBJECTIVE: To determine the relationship between serum 1, 25-dihydroxyvitamin D levels and the degree of sarcoidosis disease chronicity. DESIGN: Serum 1, 25-dihydroxyvitamin D levels were measured and associated with sarcoidosis activity and phenotypes as assessed by Sarcoidosis Severity Score and Sarcoidosis Clinical Activity Classification respectively. RESULTS: Fifty nine patients were recruited with 44% having a sub-acute onset, and the chronic disease phenotype. There was no significant difference in serum 1, 25-dihydroxyvitamin D levels by chest radiograph stage ( $p = 0.092$ ) nor did the levels correlate with the Sarcoidosis Severity Score ( $r = -0.16$ ;  $p = 0.216$ ). Serum 1, 25-dihydroxyvitamin D levels were associated with patients requiring repeated regimens of systemic immunosuppressive therapy or >1 year of therapy (SCAC Class 6). Increasing quartiles of serum 1, 25-dihydroxyvitamin D level was associated increased odds of the chronic phenotype (OR 1.82, 95% CI, 1.11, 2.99,  $p = 0.019$ ). The majority (71%) of the patients with levels >51 pg/mL required chronic immunosuppressive therapy as defined by SCAC class 6. CONCLUSIONS: In patients with sarcoidosis, elevated 1, 25-dihydroxyvitamin D levels are associated with chronic treatment needs.

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## **Pulmonary & Critical Care Medicine**

Lamb, C. R., D. Feller-Kopman, A. Ernst, M. J. Simoff, D. H. Sterman, M. M. Wahidi and K. L. Kovitz (2010). "An Approach to Interventional Pulmonary Fellowship Training." Chest **137**(1): 195-199. [PDF Full-Text](#)

[Kovitz, Kevin L.] Chicago Chest Ctr, Elk Grove Village, IL 60007 USA. [Lamb, Carla R.] Lahey Clin Fdn, Intervent Pulm Fellowship Program, Burlington, MA USA. [Feller-Kopman, David] Johns Hopkins Univ Hosp, Baltimore, MD 21287 USA. [Ernst, Armin] Beth Israel Deaconess Med Ctr, Div Cardiothorac Surg & Intervent Pulmonol, Boston, MA USA. [Simoff, Mike J.] Henry Ford Med Ctr, Detroit, MI USA. [Sterman, Daniel H.] Univ Penn, Med Ctr, Sect Intervent Pulmonol & Thorac Oncol, Pulm Allergy & Crit Care Div, Philadelphia, PA 19104 USA. [Wahidi, Momen M.] Duke Univ, Med Ctr, Div Pulm Allergy & Crit Care Med, Durham, NC USA. Kovitz, KL, Chicago Chest Ctr, 800 Biesterfield Rd, 510, Elk Grove Village, IL 60007 USA. [kovitz@chestcenter.com](mailto:kovitz@chestcenter.com)

Interventional pulmonology continues to be a specialty that is experiencing an evolution of new technologies, with an emphasis on multidisciplinary care. The diversity and application of these procedures in patients with more complex conditions is leading to the need for more specific recommendations in training within this area. As patient safety and outcomes-based measures of clinical practice and procedures are in the forefront, the need for standardization in procedural training in high-volume centers of excellence beyond pulmonary and critical care fellowships must be considered. Other procedure-based specialties have developed such training programs, with structured curricula to enhance patient safety and outcomes, develop validated metrics for competency assessment of trainees, improve trainee education, and further advance the field by fostering research. CHEST 2010; 137(1):195-199

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## **Pulmonary & Critical Care Medicine**

Swiderek, J., S. Morcos, V. Donthireddy, R. Surapaneni, V. Jackson-Thompson, L. Schultz, S. Kini and P. Kvale (2010). "Prospective Study To Determine the Volume of Pleural Fluid Required To Diagnose Malignancy." Chest **137**(1): 68-73. [PDF Full-Text](#)

[Swiderek, Jennifer; Kvale, Paul] Henry Ford Hosp, Dept Pulm & Crit Care Med, Detroit, MI 48202 USA. [Donthireddy, Vijayalakshmi] Henry Ford Hosp, Dept Hematol & Oncol, Detroit, MI 48202 USA. [Schultz, Lonni] Henry Ford Hosp, Dept Biostat, Detroit, MI 48202 USA. [Jackson-Thompson, Vicki; Kini, Sudha] Henry Ford Hosp, Dept Pathol, Detroit, MI 48202 USA. [Morcos, Samer] Windham Hosp, Dept Pulm & Sleep Med, Willimantic, CT USA. [Surapaneni, Rajesh] UMDNJ Robert Wood Johnson Cooper Univ Hosp, Dept Hematol & Oncol, New Brunswick, NJ USA. Kvale, P, Henry Ford Hosp, Dept Pulm & Crit Care Med, 2799 W Grand Blvd, Detroit, MI 48202 USA. [pkvale1@hfhs.org](mailto:pkvale1@hfhs.org)

Background: The optimal volume of pleural fluid to diagnose a malignant effusion is unknown. Our study was designed to demonstrate if a minimum pleural fluid volume (10 mL) is equivalent to a large volume thoracentesis to make a cytopathologic diagnosis of malignancy. Methods: A total of 121 thoracentesis samples were obtained from 102 patients with suspected or known malignant effusions. Pleural fluid was collected in three aliquots for cytologic examination (10 mL, 60 mL, 2 >= 150 mL). The pathologist was blinded to patient identifiers and aliquot volume. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated for each volume for the diagnosis of malignancy. Results: Pleural malignancy was diagnosed in 90 patient encounters (74.4%). For direct smear/cytospin, there was increased sensitivity and NPV for 60 mL (P = .0058 and P = .045, respectively) and for >= 150 mL (P < .001 and P = .009, respectively) compared with 1.0 mL. For combined direct smear/cytospin and cell block preparations, statistical significance for sensitivity, and NPV existed only between the 10 mL and >= 150 mL specimens (P = .0099 and P = .033, respectively). No statistical difference existed for specificity or PPV for any aliquot volume. Conclusions: The sensitivity for diagnosis of pleural malignancy is dependent on the pleural fluid volume extracted during thoracentesis. Volumes of 10 mL do not perform as well as larger volumes. When both direct smear/cytospin and cell block preparations are used, we recommend >= 150 mL, whereas when only direct smear/cytospin is used, 60 mL is adequate for the diagnosis a malignant pleural effusion. CHEST 2010; 137(1):68-73

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## **Radiation Oncology**

Bellon, M., C. Fraser, B. Sintay, I. Chetty and M. A. Elshaikh (2009). "Interfraction Geometric and Dosimetric Variations in Vaginal Cuff High Dose-rate Brachytherapy using CT Based Planning: A Prospective Study." International Journal of Radiation Oncology Biology Physics **75**(3): S381-S382. [PDF Full-Text](#)

[Bellon, M.; Fraser, C.; Sintay, B.; Chetty, I.; Elshaikh, M. A.] Henry Ford Hlth Syst, Detroit, MI USA.

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### **Radiation Oncology**

Bruner, D. W., K. Bae, F. Siddiqui, C. J. Langer, J. Coyne, V. Gamerman, R. Komaki, H. Choy, W. J. Curran and B. Movsas (2009). "The Influence of Gender, Race, and Marital Status on Survival in Lung Cancer Patients: Meta-analysis of Radiation Therapy Oncology Group (RTOG) Trials." International Journal of Radiation Oncology Biology Physics **75**(3): S163-S163. [PDF Full-Text](#)

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[Khalid, N.; Owen, J. B.; Crozier, C. L.] Amer Coll Radiol, Philadelphia, PA 53226 USA. [Movsas, B.] Henry Ford Hlth Syst, Detroit, MI USA. [Wilson, J. F.] Med Coll Wisconsin, Milwaukee, WI USA.

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### **Radiation Oncology**

Kim, J., J. Jin, N. Walls, N. Wen, D. Liu, S. H. Patel, B. Movsas, J. Rock, S. Ryu and I. J. Chetty (2009). "Dosimetric Impact of Angular Deviations in Positioning for Spinal Radiosurgery." International Journal of Radiation Oncology Biology Physics **75**(3): S673-S673. [PDF Full-Text](#)

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[Movsas, B.] Henry Ford Hosp, Detroit, MI 48202 USA. [Bae, K.] Radiat Therapy Oncol Grp, Philadelphia, PA USA. [Meyers, C.] Univ Texas Houston, MD Anderson Canc Ctr, Houston, TX 77030 USA. [Gore, E.] Med Coll Wisconsin, Milwaukee, WI 53226 USA. [Bonner, J.] Univ Alabama, Birmingham, AL USA. [Sun, A.] Ontario Canc Inst, Toronto, ON M4X 1K9, Canada. [Schild, S.] Mayo Clin, Scottsdale, AZ USA. [Gaspar, L. E.] Univ Colorado Denver, Aurora, CO USA. [Bogart, J.] SUNY Upstate Med Univ, Syracuse, NY USA. [Choy, H.] UT SW Med Ctr Dallas, Dallas, TX USA.

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Neicu, T., I. J. Cherry, D. Pradhan, H. Stricker, B. Movsas and M. Elshaikh (2009). "A Comparative Study for Daily Localization with 3D Ultrasound, Cone Beam CT, and Implanted Prostate Fiducial Markers for Patients undergoing IGRT for Prostate Cancer." International Journal of Radiation Oncology Biology Physics **75**(3): S606-S606. [PDF Full-Text](#)

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### **Radiation Oncology**

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### **Radiation Oncology**

Small, W., J. James, T. Moore, D. Fintel, S. Lutz, B. Movsas, M. Suntharalingam, Y. Graces, R. Ivker and L. Berk (2009). "A Phase II Randomized Trial with Captopril in Patients Who Have Received Radiation Therapy +/- Chemotherapy for Stage II-IIIb Non-small Cell Lung Cancer and Stage I Central Non-small Cell Lung Cancer, or Limited-stage Small-cell Lung Cancer: RTOG 0123." International Journal of Radiation Oncology Biology Physics **75**(3): S461-S462. [PDF Full-Text](#)

[Small, W.; Fintel, D.] Northwestern Univ, Sch Med, Robert H Lurie Comprehens Canc Ctr, Chicago, IL 60611 USA. [James, J.] RTOG Stat, Philadelphia, PA USA. [Moore, T.] Columbus CCOP, Columbus, OH USA. [Lutz, S.] Blanchard Valley Radiat Oncol, Findlay, OH USA. [Movsas, B.] Henry Ford Hlth Syst, Detroit, MI USA. [Suntharalingam, M.] Univ Maryland, Baltimore, MD 21201 USA. [Graces, Y.] Mayo Clin, Rochester, MN USA. [Ivker, R.] Newark Beth Israel Med Ctr, Newark, NJ USA. [Berk, L.] Moffitt, Tampa Bay, FL USA.

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### **Radiation Oncology**

Walker, E. M., A. I. Rodriguez, B. Kohn, R. M. Ball, J. Pegg, J. R. Pocock, R. Nunez, E. Peterson, S. Jakary and R. A. Levine (2010). "Acupuncture versus venlafaxine for the management of vasomotor symptoms in patients with hormone receptor-positive breast cancer: a randomized controlled trial." J Clin Oncol **28**(4): 634-40. [PDF Full-Text](#)

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**PURPOSE:** Vasomotor symptoms are common adverse effects of antiestrogen hormone treatment in conventional breast cancer care. Hormone replacement therapy is contraindicated in patients with breast cancer. Venlafaxine (Effexor), the therapy of choice for these symptoms, has numerous adverse effects. Recent studies suggest acupuncture may be effective in reducing vasomotor symptoms in menopausal women. This randomized controlled trial tested whether acupuncture reduces vasomotor symptoms and produces fewer adverse effects than venlafaxine. **PATIENTS AND METHODS:** Fifty patients were randomly assigned to receive 12 weeks of acupuncture (n = 25) or venlafaxine (n = 25) treatment. Health outcomes were

measured for up to 1 year post-treatment. RESULTS: Both groups exhibited significant decreases in hot flashes, depressive symptoms, and other quality-of-life symptoms, including significant improvements in mental health from pre- to post-treatment. These changes were similar in both groups, indicating that acupuncture was as effective as venlafaxine. By 2 weeks post-treatment, the venlafaxine group experienced significant increases in hot flashes, whereas hot flashes in the acupuncture group remained at low levels. The venlafaxine group experienced 18 incidences of adverse effects (eg, nausea, dry mouth, dizziness, anxiety), whereas the acupuncture group experienced no negative adverse effects. Acupuncture had the additional benefit of increased sex drive in some women, and most reported an improvement in their energy, clarity of thought, and sense of well-being. CONCLUSION: Acupuncture appears to be equivalent to drug therapy in these patients. It is a safe, effective and durable treatment for vasomotor symptoms secondary to long-term antiestrogen hormone use in patients with breast cancer.

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## Radiation Oncology

Walls, N. M., T. Nurushev, J. Jin, K. Levin, S. H. Patel, S. Ryu, I. J. Chetty and B. Movsas (2009). "Assessment of 2D X-ray and Volumetric-based Localization Imaging for Patients Treated with SRS and SBRT." International Journal of Radiation Oncology Biology Physics **75**(3): S682-S682. [PDF Full-Text](#)

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## Radiation Oncology

Wolfson, A., K. Bae, R. Komaki, C. Meyers, B. Movsas, C. Le Pechoux, M. Werner-Wasik, G. Videtic, Y. Garces and H. Choy (2009). "Secondary Endpoints of a Phase II Randomized Trial (RTOG 0212): Impact of Different Total Doses and Schedules of Prophylactic Cranial Irradiation on Chronic Neurotoxicity and Quality of Life for Patients with Limited Disease Small-cell Lung Cancer." International Journal of Radiation Oncology Biology Physics **75**(3): S34-S34. [PDF Full-Text](#)

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## Radiation Oncology

Zhong, H. and J. V. Siebers (2009). "Monte Carlo dose mapping on deforming anatomy." Phys Med Biol **54**(19): 5815-30. [PDF Full-Text](#)

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This paper proposes a Monte Carlo-based energy and mass congruent mapping (EMCM) method to calculate the dose on deforming anatomy. Different from dose interpolation methods, EMCM separately maps each voxel's deposited energy and mass from a source image to a reference image with a displacement vector field (DVF) generated by deformable image registration (DIR). EMCM was compared with other dose mapping methods: energy-based dose interpolation (EBDI) and trilinear dose interpolation (TDI). These methods were implemented in EGSnrc/DOSXYZnrc, validated using a numerical deformable phantom and compared for clinical CT images. On the numerical phantom with an analytically invertible deformation map, EMCM mapped the dose exactly the same as its analytic solution, while EBDI and TDI had average dose errors of 2.5% and 6.0%. For a lung patient's IMRT treatment plan, EBDI and TDI differed from EMCM by 1.96% and 7.3% in the lung patient's entire dose region, respectively. As a 4D Monte Carlo dose calculation technique, EMCM is accurate and its speed is comparable to 3D Monte Carlo simulation. This method may serve as a valuable tool for accurate dose accumulation as well as for 4D dosimetry QA.

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## Sleep Medicine

Bolge, S. C., R. Balkrishnan, H. Kannan, B. Seal and C. L. Drake (2010). "Burden associated with chronic sleep maintenance insomnia characterized by nighttime awakenings among women with menopausal symptoms." Menopause-the Journal of the North American Menopause Society **17**(1): 80-86. [PDF Full-Text](#)

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Objective: The aim of this study was to quantify the burden associated with chronic sleep maintenance insomnia characterized by nighttime awakenings (CINA) among women with menopausal symptoms. Methods: Data were obtained from the 2006 US National Health and Wellness Survey, an annual cross-sectional study of US adults 18 years or older. Analyses were limited to female respondents currently experiencing symptoms of menopause. The definition of CINA was experiencing nighttime awakenings at least twice per week for more than 1 month that have moderate to severe impact on daily life and not experiencing difficulty falling asleep. No insomnia was defined as not self-reporting insomnia, sleep difficulties, or sleep symptoms. Outcomes included resource utilization in the past 6 months, Work Productivity and Activity Impairment questionnaire.. and Medical Outcomes Study Short-Form Health Survey (SF-8.). Linear regression models were developed to assess the independent associations of CINA on outcomes, while adjusting for demographics and comorbidity. Results: Among women with menopausal symptoms, 141 met the criteria for CINA and 1,305 met the criteria for no insomnia. Adjusting for demographics and comorbidity, those experiencing CINA had 0.1 (P = 0.041) more emergency department visits, 20.8% (P < 0.001) greater activity impairment, and SF-8 physical and mental summary scores that were 4.7 (P < 0.001) and 5.4 (P < 0.001) points, respectively, lower than those of women who are not experiencing insomnia. Among women with menopausal symptoms employed full-time, those experiencing CINA had greater impairment while working (presenteeism; 17.3%, P < 0.001) and overall (16.1%, P < 0.001) than did those who are not experiencing insomnia. Conclusions: Among women with menopausal symptoms, CINA in relative isolation was associated with a significant negative impact on healthcare utilization and its associated costs, health-related quality of life, and work productivity.

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## Sleep Medicine

Palesh, O. G., J. A. Roscoe, K. M. Mustian, T. Roth, J. Savard, S. Ancoli-Israel, C. Heckler, J. Q. Purnell, M. C. Janelsins and G. R. Morrow (2010). "Prevalence, Demographics, and Psychological Associations of Sleep Disruption in Patients With Cancer: University of Rochester Cancer Center-Community Clinical Oncology Program." Journal of Clinical Oncology **28**(2): 292-298. [PDF Full-Text](#)

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Purpose Sleep disruption is prevalent in patients with cancer and survivors, but the prevalence of insomnia, a distressing sleep disorder, in these populations has yet to be determined in large-scale studies. Patients and Methods A total of 823 patients with cancer receiving chemotherapy (mean age, 58 years; 597 female patients) reported on sleep difficulties in a prospective study. Results During day 7 of cycle 1 of chemotherapy, 36.6% (n = 301) of the patients with cancer reported insomnia symptoms, and 43% (n = 362) met the diagnostic criteria for insomnia syndrome. Patients with cancer younger than 58 years were significantly more likely to experience either symptoms of insomnia or insomnia syndrome (chi(2) = 13.6; P = .0002). Patients with breast cancer had the highest number of overall insomnia complaints. A significant positive association was found between symptoms of insomnia during cycles 1 and 2 of chemotherapy (phi = .62, P < .0001), showing persistence of insomnia during the first two cycles of chemotherapy. Sixty percent of the patient

sample reported that their insomnia symptoms remained unchanged from cycle 1 to cycle 2. Those with insomnia complaints had significantly more depression and fatigue than good sleepers (all  $P < .0001$ ). Conclusion The proportions of patients with cancer in this sample reporting symptoms of insomnia and meeting diagnostic criteria for insomnia syndrome during chemotherapy are approximately three times higher than the proportions reported in the general population. Insomnia complaints persist throughout the second chemotherapy cycle for the majority of patients with cancer in this study. Insomnia is prevalent, underrecognized, undermanaged, and understudied among patients with cancer receiving chemotherapy.

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## Sleep Medicine

Roth, T. (2009). "Slow wave sleep: does it matter?" *J Clin Sleep Med* **5**(2 Suppl): S4-5.

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## Surgery

Deeb, D., X. H. Gao, H. Jiang, B. Janic, A. S. Arbab, Y. Rojanasakul, S. A. Dulchavsky and S. C. Gautam (2010). "Oleanane triterpenoid CDDO-Me inhibits growth and induces apoptosis in prostate cancer cells through a ROS-dependent mechanism." *Biochemical Pharmacology* **79**(3): 350-360. [Article Request Form](#)

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CDDO-Me, a synthetic triterpenoid derived from oleanolic acid, is a promising anticancer agent that has shown strong activity against a wide variety of cancer types in vitro and in vivo. We have previously shown that CDDO-Me induces apoptosis in prostate cancer cells irrespective of their hormonal status. To further understand the proapoptotic mechanism of CDDO-Me, we investigated the role of reactive oxygen species (ROS) in mediating the apoptosis inducing activity of CDDO-Me in LNCaP and PC-3 prostate cancer cell lines. Here, we show that CDDO-Me induces ROS generation from both nonmitochondrial and mitochondrial sources, which is associated with the induction of apoptosis as characterized by increased annexin V-binding, cleavage of PARP-1 and procaspases-3, -8, -9, loss of mitochondrial membrane potential and release of cytochrome c. In addition, CDDO-Me inhibited cell survival Akt, NF-kappa B and mTOR signaling proteins. The inhibition of ROS generation by N-acetylcysteine (NAC) or by overexpression of antioxidant enzymes glutathione peroxidase (GPx) and superoxide dismutase-1 (SOD-1) prevented CDDO-Me-induced apoptosis. Pretreatment with NAC blocked annexin V-binding, cleavage of PARP-1 and procaspases-3, -8, -9, loss of mitochondrial membrane potential and release of cytochrome c by CDDO-Me. NAC also prevented the inhibition of constitutively active Akt, NF-kappa B and mTOR by CDDO-Me. Together, these data indicate that ROS plays an essential role in the induction of apoptosis by CDDO-Me in prostate cancer cells. (C) 2009 Elsevier Inc. All rights reserved.

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## Surgery

Gao, X., D. Deeb, Y. Liu, S. Gautam, S. A. Dulchavsky and S. C. Gautam (2009). "Immunomodulatory activity of xanthohumol: inhibition of T cell proliferation, cell-mediated cytotoxicity and Th1 cytokine production through suppression of NF-kappaB." *Immunopharmacol Immunotoxicol* **31**(3): 477-84. 2759314. [Article Request Form](#)

Division of Surgical Research, Department of Surgery, Henry Ford Health System, Detroit, Michigan, USA.

Xanthohumol (XN), a prenylated chalcone present in hops (*Humulus lupulus* L.) and beer, exhibits anti-inflammatory, antioxidant and antiproliferative activity, but has not been studied for effects on T cell-mediated immune responses. Here we demonstrate that XN has profound immunosuppressive effects on T cell

proliferation, development of IL-2 activated killer (LAK) cells, cytotoxic T lymphocytes (CTLs), and production of Th1 cytokines (IL-2, IFN-gamma and TNF-alpha). The suppression of these cell-mediated immune responses by XN was at, least in part, due to the inhibition of nuclear factor kappa B (NF-kappaB) transcription factor through suppression of phosphorylation of IkappaBalpha, an inhibitor of NF-kappaB.

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## **Surgery**

Liptay, M. J., S. Basu, M. C. Hoaglin, N. Freedman, L. P. Faber, W. H. Warren, Z. T. Hammoud and A. W. Kim (2009). "Diffusion Lung Capacity for Carbon Monoxide (DLCO) Is an Independent Prognostic Factor for Long-Term Survival After Curative Lung Resection for Cancer." Journal of Surgical Oncology **100**(8): 703-707. [Article Request Form](#)

[Liptay, Michael J.] Rush Univ, Med Ctr, Div Thorac Surg, Chicago, IL 60612 USA. [Hoaglin, Michael C.; Freedman, Neil] N Shore Univ Hlth Syst, Evanston, IL USA. [Hammoud, Zane T.] Henry Ford Hosp, Detroit, MI 48202 USA. Liptay, MJ, Rush Univ, Med Ctr, Div Thorac Surg, 1725 W Harrison St, Suite 774, Chicago, IL 60612 USA. [michael\\_liptay@rush.edu](mailto:michael_liptay@rush.edu)

Introduction: We examined the early and late prognostic significance of DLCO and forced expiratory volume in 1 sec (FEV1) in patients who underwent surgical resection of lung cancer. Methods: From 1997 to 2004, 462 patients underwent successful complete resection of their lung cancer and had full pulmonary function testing including DLCO performed. Mean follow-up was over 5 years (64.8 months-range: 0-158 months). Results: Postoperative 90-day mortality was 2.6% (12/462). At last follow-up, of the remaining 450 patients, 182 patients were alive, 130 had died of cancer, and 138 have died of other causes and did not have recurrent cancer. Mean DLCO values were 69.4%, 66.8%, and 53.9%, respectively. Mean FEV1 values were 81.3%, 78.1%, and 71.5%, respectively. Mean DLCOs and FEV1s between patients who died of cancer versus other causes were significantly different (P < 0.0001 and P = 0.0157). When cause-specific survival was analyzed for both DLCO and FEV1 Simultaneously, DLCO had a very significant effect on survival from other causes (HR 0.966, P < 0.0001) when adjusted for FEV1. However, when adjusted by DLCO, FEV1 had no significant effect. A DLCO <40% best predicted decreased survival from causes other than cancer within stage I lung cancers (stage IA H R 0.953, P < 0.0001; stage TB. HR 0.968, P < 0.0001). Conclusions: DLCO was found to be a significant prognostic factor for long-term survival after lung cancer surgery. This may serve as a surrogate for competing morbidities with declining values predicting a higher risk of late non-cancer-related death. J. Surg. Oncol. 2009;100:703-707. (C) 2009 Wiley-Liss, Inc.

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## **Surgery**

Von Riedenauer, W. B., R. W. Cutsinger, X. L. Jing, S. D. Berry, S. Maqusi and N. A. Silverman (2010). "Posttraumatic pericardiobiliary fistula causing acute bilious pericardial tamponade." J Trauma **68**(1): E8-E10. [PDF Full-Text](#)

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## **Urology**

Bai, V. U., S. Murthy, K. Chinnakannu, F. Muhletaler, S. Tejwani, E. R. Barrack, S. H. Kim, M. Menon and G. P. Veer Reddy (2010). "Androgen regulated TRPM8 expression: a potential mRNA marker for metastatic prostate cancer detection in body fluids." Int J Oncol **36**(2): 443-50. [Article Request Form](#)

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI 48202, USA.

Identification of sensitive and specific biomarkers for early detection and prognosis of prostate cancer is essential for timely and appropriate treatment of the disease in individual patients. We identified an RNA transcript with sequence homology to TRPM8 (melastatin-related transient receptor potential member 8) that was overexpressed in tumor vs. patient-matched non-tumor prostate tissues by RT-PCR differential display (DD). Semi-quantitative RT-PCR analysis revealed that TRPM8 levels were higher in tumor than in non-tumor tissue from 31 of 40 (>75%) patients examined. Overexpression of TRPM8 was independent of changes in androgen receptor (AR) mRNA levels in tumor tissue. However, in studies with established cell lines, TRPM8

expression was detectable only in AR-positive, but not in AR-negative cells, and it was suppressed by steroid deprivation or anti-androgen bicalutamide (Casodex) treatment, suggesting the requirement of AR activity for TRPM8 expression in prostate cancer cells. TRPM8 mRNA was also detected in body fluids of men. Most importantly, its levels were significantly higher ( $p < 0.001$ ,  $n = 18$ ) in urine and blood of patients with metastatic disease than in those of healthy men. However, there was no significant difference ( $p > 0.05$ ,  $n = 10$ ) in its levels between prostate cancer patients with localized disease and healthy men. Together, these studies demonstrate that TRPM8 expression is androgen regulated in prostate cancer cells and that, while tissue TRPM8 mRNA levels can be used for detection of prostate cancer, urine and blood TRPM8 mRNA levels may prove to be useful for distinguishing metastatic disease from clinically localized prostate cancer at the time of diagnosis.

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## Urology

Patel, M. N., S. A. Kaul, A. Bhandari, M. Menon, J. O. Peabody, J. S. Elder and C. G. Rogers (2010). "Robot-Assisted Management of Congenital Renal Abnormalities in Adult Patients." J Endourol **EPub Ahead of Print**. [PDF Full-Text](#)

Vattikuti Urology Institute , Henry Ford Hospital, Detroit, Michigan.

**Abstract Introduction:** Congenital anomalies of the genitourinary tract are usually diagnosed and corrected in childhood. Robot-assisted management of congenital urologic abnormalities in adult patients has not been described previously. We present a series of patients with congenital renal abnormalities diagnosed in adulthood and managed using a robotic approach. **Methods:** Four patients at our institution were identified with congenital renal abnormalities diagnosed in adulthood. One had a duplicated collecting system with hydronephrosis of a thinned out upper pole moiety and underwent heminephroureterectomy. A second had right hydronephrosis, complete atrophy of the right renal cortex, and a dilated tortuous ureter with obstructing ureterocele and underwent simple nephrectomy. A third patient had a duplicated system with distal ureteral reflux and an ureterocele and underwent ureteroureterostomy and distal ureterectomy. The fourth had a duplicated collecting system with ureterovaginal fistula of the upper pole moiety. **Perioperative variables** were collected including operative time, estimated blood loss, length of hospital stay, and change in estimated creatinine clearance. **Results:** Mean age was 35 years (range 16-54), mean body mass index was 30.9 kg/m<sup>2</sup> (21.8-42.5), and mean baseline estimated creatinine clearance was 147.7 mL/minutes (107.7-214.6). Mean operative time was 258 minutes (151-374) and mean estimated blood loss was 44 mL (25-50). Postoperative estimated creatinine clearance was 133.1 mL/minutes (115.9-160.9), which was not statistically different from preoperative values ( $p = 0.608$ ). All patients were discharged by postoperative day 2. There were no perioperative complications. **Conclusions:** Robot-assisted management of congenital renal abnormalities is a feasible and efficacious treatment modality in adult patients with low morbidity and good outcomes.

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## Urology

Patel, M. N., L. S. Krane, A. Bhandari, R. G. Laungani, A. Shrivastava, S. A. Siddiqui, M. Menon and C. G. Rogers (2010). "Robotic Partial Nephrectomy for Renal Tumors Larger Than 4 cm." European Urology **57**(2): 310-316. [PDF Full-Text](#)

[Patel, Manish N.; Krane, L. Spencer; Bhandari, Akshay; Laungani, Rajesh G.; Shrivastava, Alok; Siddiqui, Sameer A.; Menon, Mani; Rogers, Craig G.] Henry Ford Hosp, Vattikuti Urol Inst, Detroit, MI 48202 USA. Rogers, CG, Henry Ford Hosp, Vattikuti Urol Inst, 2799 W Grand Blvd, Detroit, MI 48202 USA. [crogers2@hfhs.org](mailto:crogers2@hfhs.org)

**Background:** Minimally invasive partial nephrectomy (PN) is most commonly performed for renal tumors  $\leq 4$  cm in size. Robotic PN (RPN) for tumors  $>4$  cm has not been assessed. **Objective:** To evaluate the safety and feasibility of RPN for tumors  $>4$  cm in the context of patients undergoing RPN for tumors  $\leq 4$  cm. **Design, setting, and participants:** We reviewed data for 71 consecutive patients who underwent transperitoneal RPN at a tertiary care center between August 2007 and September 2009 by a single surgeon. Patients were stratified into two groups: 15 with tumors  $>4$  cm on preoperative imaging (group 1) and 56 patients with tumors  $\leq 4$  cm (group 2). **Intervention:** All patients underwent transperitoneal RPN by a single surgeon. **Measurements:** Preoperative, perioperative, pathologic, and functional outcomes data were analyzed and compared between groups. We used  $\chi^2$  and student t tests for categorical and continuous variables, respectively. A p value

<0.05 was considered statistically significant. Results and limitations: Mean radiographic tumor size was 5.0 cm (4.1-7.9) for group 1 and 2.1 cm (0.7-3.8) for group 2. No significant differences were found between groups for estimated blood loss, total operative time, hospital stay, complication rates, and change in estimated glomerular filtration rate. Patients with larger tumors had longer median warm ischemia times (25 vs 20 min;  $p = 0.011$ ). Limitations of our study include the retrospective nature the analysis, small sample size, and single-surgeon experience. Conclusions: In our initial experience, RPN for tumors >4 cm is safe and feasible, showing comparable outcomes to RPN for smaller tumors, although with longer warm ischemia times. Future studies with extended follow-up are necessary to determine the viability of RPN for large tumors as an effective form of treatment. (c) 2009 European Association of Urology. Published by Elsevier B.V. All rights reserved.

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## Urology

Sammon, J., A. Perry, L. Beaulé, T. Kinkead, D. Clark and M. Hansen (2010). "Robot-assisted radical prostatectomy: learning rate analysis as an objective measure of the acquisition of surgical skill." *BJU Int* **EPub Ahead of Print**. [Article Request Form](#)

Urology, Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA.

Study Type - Therapy (case series) Level of Evidence 4 OBJECTIVE To adapt an industrial definition of learning-curve analysis to surgical learning, and elucidate the rate at which experienced open surgeons acquire skills specific to robot-assisted radical prostatectomy (RARP) at a community-based medical centre. PATIENTS, SUBJECTS AND METHODS The total procedure time (TPT) of the first 75 RARPs, performed by three surgeons experienced with retropubic RP, was analysed to determine the point at which their learning rate stabilised. Operative characteristics were compared before and after this point to isolate the plateau of learning rate as a mark of acquiring surgical skill. The operative characteristics examined were TPT, estimated blood loss (EBL), bladder neck contractures (BNC), positive margins (PM) and length of hospital stay (LOS). RESULTS The mean rate of TPT decrease, for procedures 1-75, was 13.4% per doubling of RARPs performed. After the first 25 procedures the TPT decreased at a rate of 1.8% per doubling, not significantly different from 0 ( $P > 0.05$ ). There was no significant difference between procedures 1-25 and 26-75 in rates of EBL, BNC and PM. There was a significant change for all surgeons in TPT, with a mean of 303.1 min (RARPs 1-25) vs 213.6 min (26-75) ( $P < 0.001$ ), and LOS, of 2.1 days (1-25) vs 1.4 days (26-75) ( $P < 0.001$ ). CONCLUSIONS An industrial definition of learning-curve analysis can be adapted to provide an objective measure of learning RARP. The average learning rate for RARP was found to plateau by the 25th procedure. Also, the learning rate plateau can serve as an objective measure of the acquisition of surgical skill.

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## Urology

Touijer, K., D. Jacqmin, L. R. Kavoussi, F. Montorsi, J. J. Patard, C. G. Rogers, P. Russo, R. G. Uzzo and H. Van Poppel (2010). "The Expanding Role of Partial Nephrectomy: A Critical Analysis of Indications, Results, and Complications." *European Urology* **57**(2): 214-222.

[PDF Full-Text](#)

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Context: The gained expertise in the surgical technique of partial nephrectomy (PN) with excellent oncologic outcome and reduced morbidity has contributed to more frequent use of PN in many centres of reference, and the recent evidence favouring PN over radical nephrectomy (RN) in the prevention of chronic kidney disease and possibly linking it to a better overall survival (OS) will constitute a strong argument for wider use of PN. Objective: To objectively analyse the advantages of PN over RN and to evaluate the risk-benefit ratio of expanding the indications of PN T1b renal cortical tumours. Evidence acquisition: Literature searches on

English-language publications were performed using the National Library of Medicine database. The queries included the keywords partial nephrectomy and nephron sparing surgery. Eight hundred four references were scrutinised, and 175 publications were identified and reviewed. Sixty-nine articles were selected for this review. These references formed the basis for this analysis and were selected based on their relevance and the importance of their content. Evidence synthesis: The use of PN has been steadily increasing, particularly in tertiary care centres. This trend is now strengthened by evidence supporting the role of PN in reducing the risk of chronic kidney disease in patients with renal masses  $\leq 4$  cm. A wider use of PN for larger tumours, granted technical feasibility, is supported by the preliminary evidence, suggesting an OS advantage favouring PN over RN. However, the potential for selection bias and residual confounding factors may contribute to the observed difference. In the carefully selected patients with tumours  $>4$  cm, PN obtained equivalent oncologic outcome to that achieved after RN. Although higher morbidity rates were seen after PN, the complication type and severity were not prohibitive. Conclusions: The available evidence supports elective PN as the standard surgical treatment for renal cortical tumours  $\leq 4$  cm. For larger tumours, PN has demonstrated feasibility and oncologic safety in the carefully selected patient population studied. (C) 2009 European Association of Urology. Published by Elsevier B. V. All rights reserved.

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## Urology

Walz, J., A. L. Burnett, A. J. Costello, J. A. Eastham, M. Graefen, B. Guillonnet, M. Menon, F. Montorsi, R. P. Myers, B. Rocco and A. Villers (2010). "A Critical Analysis of the Current Knowledge of Surgical Anatomy Related to Optimization of Cancer Control and Preservation of Continence and Erection in Candidates for Radical Prostatectomy." European Urology 57(2): 179-192. [PDF Full-Text](#)

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Context: Detailed knowledge of the anatomy of the prostate and adjacent tissues is mandatory during radical prostatectomy to ensure reliable oncologic and functional outcomes. Objective: To review critically and to summarize the available literature on surgical anatomy of the prostate and adjacent structures involved in cancer control, erectile function, and urinary continence. Evidence acquisition: A search of the PubMed database was performed using the keywords radical prostatectomy, anatomy, neurovascular bundle, fascia, pelvis, and sphincter. Relevant articles and textbook chapters were reviewed, analyzed, and summarized. Evidence synthesis: Anatomy of the prostate and the adjacent tissues varies substantially. The fascia surrounding the prostate is multilayered, sometimes either fused with the prostate capsule or clearly separated from the capsule as a reflection of interindividual variations. The neurovascular bundle (NVB) is situated between the fascial layers covering the prostate. The NVB is composed of numerous nerve fibers superimposed on a scaffold of veins, arteries, and variable amounts of adipose tissue surrounding almost the entire lateral and posterior surfaces of the prostate. The NVB is also in close, cage-like contact to the seminal vesicles. The external urethral sphincter is a complex structure in close anatomic and functional relationship to the pelvic floor, and its fragile innervation is in close association to the prostate apex. Finally, the shape and size of the prostate can significantly modify the anatomy of the NVB, the urethral sphincter, the dorsal vascular complex, and the pubovesical/puboprostatic ligaments. Conclusions: The surgical anatomy of the prostate and adjacent tissues involved in radical prostatectomy is complex. Precise knowledge of all relevant anatomic structures facilitates surgical orientation and dissection during radical prostatectomy and ideally translates into both superior rates of cancer control and improved functional outcomes postoperatively. (C) 2009 European Association of Urology. Published by Elsevier B. V. All rights reserved.