UW Medicine
SCHOOL OF MEDICINE

Department of Surgery

presents

The Fifteenth Annual Resident Research Symposium

Friday, February 20, 2009
7:45am – 1:00pm

The Museum of History and Industry
2700 24th Avenue East
Seattle
206-324-1126

SCHEDULE OF PRESENTATIONS

Moderators: Michael Mulholland and Alexander Clowes

7:45am	Introduction	Dr. Carlos Pellegrini and Dr. Alec Clowes
8:00am	Merry	Cytokines in lung reperfusion injury
8:15am	Keech	Validating the use of siRNA as a novel technique for cell specific target gene knockdown in lung ischemia-reperfusion injury
8:30am	FitzSullivan	LPS preconditioning confers ischemic tolerance in the lung through a MYD88-independent pathway
8:45am	Smith	Mesenchymal stem cells regulate dermal fibroblast responses to injury
9:00am	Ramos	Functional genomics in fibroproliferative scarring
9:15am	Keys	Why flaps fail: predictors of pressure ulcer recurrence
9:30am	Carter	Topical P38 MAPK inhibition attenuates burn wound inflammatory signaling and reduces systemic inflammation and acute lung injury: a study of the effects of timing of application
9:45am	Grabski	S1P regulates expression of smooth muscle α-Actin by S1P2 mediated activation of Rho and calcium mobilization
10:00am	Kohler	Omeprazole induces cell death in gastric glands through a thiol oxidation pathway
10:15am	**BREAK**	
10:30am	Lao	Outcomes in children with intestinal failure following listing for intestinal transplant
10:45am	Quiroga	Morbidity and mortality in patients with ruptured abdominal aortic aneurysms: improving outcomes with a modified approach
11:00am	Soares	Endoluminal treatment of obesity: how a novel endoscopic suturing device may change the face of bariatric surgery
11:15am	Zonies	Global survey of trauma & burn education
11:30am	Mosier	Early acute kidney injury is associated with progressive renal dysfunction and increased mortality in severely burned adults
11:45am	Hassan	Association between administration of aged blood and severity of organ failure in trauma patients
12:00pm	Hamlat	Recombinant activated factor VII in trauma
12:15pm	Mandell S.	Mortality and injury patters association with roof crush in rollover crashes
12:30pm	Massarweh	Significance of discharge to skilled care following abdominopelvic surgery in older adults
12:45pm	Farjah	Surgeon specialty and long-term survival following pulmonary resection for lung cancer

3:30pm **HELEN &JOHN SCHILLING LECTURE – Hogness Auditorium, UW HSB**
Hypothalamic - Gastric Control of Food Intake
Michael Mulholland, M.D.
Chair, University of Michigan Department of Surgery

CYTOKINES IN LUNG REPERFUSION INJURY

Merry H, Keech J, Wolf P, FitzSullivan E, Mulligan M

In the earliest moments of reperfusion after lung ischemia, there is a burst of pro-inflammatory cytokine production, such as TNF and IL-1, by the alveolar macrophage. It is in the rich cytokine milieu that secondary activation of endothelial and epithelial cells likely occurs. In the later phases of lung reperfusion injury negative feedback pathways and inhibitory cytokines, such as IL-10, predominate.

Our lab has characterized the predominate cytokines produced and secreted in the alveolar space in lung reperfusion injury using a rat model of warm lung ischemia and reperfusion. Additional studies using a cell culture model of hypoxia and reoxygenation have been used to characterize the individual secretory responses of alveolar macrophages, endothelial and epithelial cells. Media transfer experiments demonstrate a clear ability of alveolar macrophage products to amplify the response of endothelial and epithelial cells to hypoxia and reoyxgenation, where as the converse was not seen.

Chelation studies were subsequently carried out and demonstrate the requirement of TNF and IL-1 within the alveolar macrophage products for this amplification to occur. Interestingly, with removal of TNF or IL-1 from the alveolar macrophage products there was suppression of the endothelial and epithelial primary response to hypoxia and reoxygenation. We hypothesize that this is due to the presence of regulatory and anti-inflammatory cytokines, such as IL-6 and IL-10, that account for this protective effect.

VALIDATING THE USE OF siRNA AS A NOVEL TECHNIQUE FOR CELL SPECIFIC TARGET GENE KNOCKDOWN IN LUNG ISCHEMIA-REPERFUSION INJURY

Keech J, FitzSullivan E, Merry H, Wolf P, Mulligan M

Background: Short interfering RNA (siRNA) has been reported as an effective method for transient knockdown of various target genes *in vitro* and *in vivo*. Despite acceptance of siRNA as a valid method *in vitro*, several issues surround *in vivo* siRNA use. Specifically, concerns have been raised regarding design, administration, efficacy, specificity and the immunostimulatory potential, or off-target effects (OTE), of siRNA *in vivo*, and the potential influence on readouts of therapeutic efficacy. There have been no studies using this technique in models of lung ischemia reperfusion injury (LIRI). Furthermore, LIRI has a predictable time of onset with the potential for practical pretreatment, where siRNA may be well suited for this purpose. A number of studies have demonstrated significant and effective uptake of intravenously administered siRNA by resident tissue inflammatory cells, including alveolar macrophages, and in addition, we have previously demonstrated the central importance of the AM in the development of LIRI. Here we describe the validation of siRNA as a novel technique for cell specific target gene knockdown in the AM in our model of LIRI.

Methods: To determine the lowest effective dose of siRNA, rats received between 1 and 50nM siRNA (TLR-4, TLR-2, MyD88), vector control or saline control intravenously in a cationic lipid vector prior to initiation of the IR protocol. Primary cultures of AM, PAEC, and T2P received between 10 and 1000pM siRNA with similar controls prior to our hypoxia reoxygenation (HR) protocol. 3 distinct, non-overlapping sequences for TLR-4, TLR-2 and MyD88 siRNA were tested for efficacy. Whole lung homogenates, individual cell populations eluted from lungs, and cell culture lysates were harvested for total protein to assess target protein knockdown by Western blot analysis. Serum from rats and media from cell cultures was assessed for IFNγ and IFNβ production after siRNA administration. Biotin labeled TLR-4 siRNA was used to assess siRNA uptake *in vitro* and distribution in the lung by IHC.

Results: Rats pretreated with TLR-4 siRNA had a 70-92% reduction in TLR-4 protein expression, and demonstrated significant protection from LIRI. When individual cell populations were eluted from lungs and whole blood from animals treated with TLR-4 siRNA there was a greater than 90% reduction in TLR-4 protein expression in AM. There was no reduction in TLR-4 expression in PAEC, T2P or WBC after *in vivo* TLR-4 siRNA. Biotin labeled TLR-4 siRNA exclusively localized to AM in the lung. There was >80% knockdown of TLR-4 expression in cultured AM, PAEC, and T2P treated with TLR-4 siRNA. All 3 cell types demonstrated uptake of biotin labeled siRNA by 6 hours. Dose response experiments determined the lowest effect dose of siRNA to be 10nM *in vivo* and 100pM/well *in vitro*. There was no significant change in IFNγ or IFNβ (Type 1 and 2 IFN, respectively) production between TLR-4, TLR-2 or MyD88 siRNA, vector or saline control treated rats or AM. All three TLR-4, TLR-2 and MyD88 siRNA sequences (9 in total) were able to effectively and specifically knockdown their respective encoded protein expression. (76-95% *in vitro*).

Conclusions: We have demonstrated the cell specific uptake of intravenously administered siRNA to the AM in the lung, and employed a series of controls for OTE, validating the efficacy, specificity and immunostimulatory potential with low dose siRNA in our model of LIRI. These results significantly increase the confidence with which the observed phenotype (protection from IR or HR) can be ascribed to knockdown of the target protein, and provide a tool for studying the central role of the AM in the development of LIRI. The incorporation of strict controls for all siRNA experiments, especially those assessing OTE, is of paramount importance toward validating experimental results and conclusions.

LPS PRECONDITIONING CONFERS ISCHEMIC TOLERANCE IN THE LUNG THROUGH A MYD88-INDEPENDENT PATHWAY

FitzSullivan E, Keech JC, Wolf PS, Merry HE, Mulligan MS

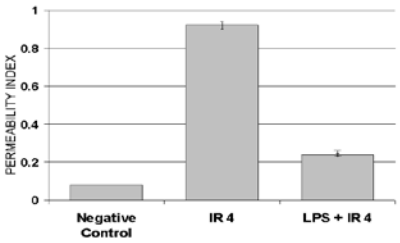
Background: Lung transplantation is an effective treatment for select patients with end-stage pulmonary disease, yet availability of donor organs remains a barrier to transplantation. While overt infection is considered a contraindication, the implications of an isolated positive gram stain remain unclear. LPS, the best known ligand for TLR-4, has been shown to induce acute lung injury in high doses, while paradoxically, low doses protect against subsequent lung ischemia reperfusion injury (LIRI). TLR-4 classically initiates signaling through recruitment of the adaptor protein MyD88, but can also initiate a MyD88 independent signaling pathway, reducing proinflammatory signaling and leading to type 1 interferon responses and Il-10 production, which are protective in LIRI.

Hypothesis: We hypothesize that LPS preconditioning alters the TLR-4 signaling response to oxidative stress by signaling through a MyD88-independent pathway, thereby conferring ischemic tolerance.

Methods: Rats were pretreated with intravenous MyD88 or TLR-4 siRNA in a lipid vector 48 hours prior to low dose intratracheal LPS installation and prior to left lung ischemia and reperfusion (IR). Following reperfusion, lungs were assessed for vascular permeability, cytokine content, MAPK activation and target protein knockdown.

Results: LPS pretreatment followed by the IR protocol led to a 74% reduction in vascular permeability ($p<0.05$), a greater than 90% reduction in CINC and TNF-α secretion ($p<0.001$), and an 80% reduction in both JNK and p38 phosphorylation ($p<0.05$), compared to positive controls. LPS pretreatment without IR yielded results equivalent to negative controls. MyD88 knockdown did not diminish the protective effect of LPS pretreatment, whereas TLR-4 knockdown did eliminate the protective effect. Western blotting confirmed effective knockdown of MyD88 and TLR-4.

Conclusions: Low dose LPS significantly reduced endothelial dysfunction and inflammatory mediator production following subsequent exposure to IR. This work is the first to describe a functionally relevant, protective effect of LPS preactivation on LIRI through a MyD88-independent pathway. Understanding the protective effect of LPS preconditioning has the potential to expand and clarify donor inclusion criteria.



Vascular permeability with LPS preconditioning. LPS pretreatment (LPS +IR4) reduced LIRI by 74% compare to positive controls (IR4), as assessed by vascular permeability.

MESENCHYMAL STEM CELLS REGULATE DERMAL FIBROBLAST RESPONSES TO INJURY

Smith A, Muffley L, Willis E, Isik F, Gibran N, Hocking A

Background: Bone marrow is a rich source of pluripotent cells identifiable as two distinct lineages: the hematopoietic population, and the mesenchymal population that is capable of differentiation into multiple cell lineages. There is much interest in the potential therapeutic applications of mesenchymal stem cells in cutaneous wound repair. We have previously shown that bone marrow-derived mesenchymal stem cells maintain a stable presence in the dermis during wound repair. However, little is known about the interactions of mesenchymal stem cells with fibroblasts, the predominant cell type of the dermis. It remains to be determined if mesenchymal stem cells regulate fibroblast responses to injury, such as migration, proliferation, and production of growth factors, cytokines, and extracellular matrix.

Purpose: To determine the effects of mesenchymal stem cells on dermal fibroblast proliferation, migration, and expression of genes important in wound repair.

Methods: Primary human dermal fibroblasts were co-cultured with murine bone marrow-derived mesenchymal stem cells grown in inserts, which allowed for paracrine interaction without direct cell contact. As controls, fibroblasts were cultured with either empty inserts or inserts containing dermal fibroblasts. Using this co-culture system, the effect of mesenchymal cells on dermal fibroblast migration was determined in a scratch wound assay and a chemotaxis assay. The effect of mesenchymal stem cells on dermal fibroblast proliferation was also analyzed. Real time PCR was used to quantify mesenchymal stem cell mediated changes in expression levels of collagens, growth factors, inflammatory cytokines and matrix metalloproteinases by dermal fibroblasts.

Results: Dermal fibroblast migration was significantly increased in the presence of mesenchymal stem cells by day 1 after scratching compared to migration with control inserts. This enhanced migration was also observed at day 2 and day 3. Scratch wound closure was complete by day 3 when the dermal fibroblasts were co-cultured with mesenchymal stem cells; in contrast controls required at least 4 days. A chemotaxis assay also revealed that dermal fibroblasts migrate towards mesenchymal stem cells. Preliminary data suggests that fibroblast proliferation is not affected by the presence of mesenchymal stem cells. Mesenchymal stem cells induced dermal fibroblasts to down-regulate expression of collagen types I and III, transforming growth factor beta-3, matrix metalloproteinases 2, 3 and 7, and interleukin 6; and up-regulate the expression of interleukin 8.

Conclusion: Mesenchymal stem cells induce dermal fibroblast migration and chemotaxis. These data suggest that mesenchymal stem cells provide an important early signal for dermal fibroblast migration into cutaneous wounds.

FUNCTIONAL GENOMICS IN FIBROPROLIFERATIVE SCARRING

Ramos M, Zhu K, Tuggle C, Honavar V, Numhom S,
Carrougher G, Gibran N, Engrav L

Introduction: Hypertrophic scarring remains a devastating problem after burn injury and we have no real understanding of etiology, control and prevention. The Duroc (fibroproliferative)/Yorkshire (nonfibroproliferative) porcine model of scarring has been validated for clinical, histological, immunohistochemical and molecular similarity to human hypertrophic scar. We are now performing functional genomics studies of microarray data obtained from the Duroc/Yorkshire model including expression clustering, gene ontology clustering and pathway analysis, to reveal prospective regulatory pathways of fibroproliferative scarring. Herein we report findings from gene ontology clustering.

Method: Shallow and deep wounds on the backs of Duroc and Yorkshire pigs were biopsied at 1, 2, 3, 12 and 20 weeks. Laser capture microdissection was used to select cells from the dermal cones and RNA from these cells was extracted, amplified and hybridized on Affymetrix Porcine GeneChips®. 123 probe sets with known human homologs were differentially over or under expressed at 3-20 weeks including nine collagen genes. We used gene ontology web tools (DAVID - Database for Annotation, Visualization and Integrated Discovery, GOMINER and FATIGO) to identify enriched biological process and molecular functions, suggesting a relationship to the fibroproliferative process, with p-value ≤ 0.05. We used the porcine transcriptome of 9,277 genes with expression on the porcine GeneChip® for the background.

Results: The selected significant biological processes and molecular functions in differentially over expressed genes are listed in Table 1. There were no significant ontology terms associated with the differentially under expressed genes.

ONTOLOGY TERM	GENES	P-VALUE
GO:0005201~extracellular matrix structural constituent	COL3A1 COL4A2 LUM COL5A3 LAMA4 COL1A2 COL14A1	5E-12
GO:0005198~structural molecule activity	COL3A1 VIM COL4A2 LUM COL5A3 LAMA4 COL1A2 COL14A1	2E-05
GO:0030199~collagen fibril organization	COL3A1 LUM COL5A2 COL14A1	2E-03
GO:0030198~extracellular matrix organization and biogenesis	COL3A1 COL4A2 LUM COL5A2 COL14A1	2E-03
GO:0004867~serine-type endopeptidase inhibitor activity	SERPING1 SERPINF1	2E-03

Table1: Enriched ontology terms in the differentially over expressed genes

Conclusion: These findings indicate that LUM (lumican), LAMA4 (laminin, alpha4), VIM (vimentin), SERPING1 (serpin peptidase inhibitor, clade G) and SERPINF1 (serpin peptidase inhibitor, clade F) need to be explored further with expression clustering and pathways analysis. They also suggest that the defective fibrillogenesis may be involved. We will use these clues to develop potential regulatory pathways of fibroproliferative scarring.

WHY FLAPS FAIL: PREDICTORS OF PRESSURE ULCER RECURRENCE

Keys K, Daniali L, Warner K, Mathes D

Background: Pressure ulcers are estimated to be present in greater one-third of the 250,000 Americans with spinal cord injury. Pressure ulcers are one of the leading causes of unplanned hospitalization after SCI, and account for more hospital days than any other complication. The rate of pressure ulcer recurrence after flap surgery has been reported on extensively over the last fifty years, ranging between 15% and 82%, with no trend towards improvement through the decades. Naturally, predictors of failure have been sought through compilation and retrospective analysis of patient data; however previous studies have failed to demonstrate statistical correlation.

Purpose: To identify and evaluate pre-operative patient and wound characteristics associated with the recurrence of pressure ulcers after operative flap coverage.

Methods: A retrospective chart review was performed on all patients who underwent flap coverage of a pressure ulcer at the Puget Sound Veterans' Affairs Hospital between 1993 and 2008. We examined 31 patient and operative variables potentially associated with pressure ulcer recurrence after flap surgery using univariate analysis. Since many patients had multiple flaps, multivariate regression with generalized estimating equation analysis was used to determine the effect of factors associated with recurrence identified in our univariate analysis. The primary outcome was recurrence of pressure ulcer at the operative site. Secondary outcomes included flap line dehiscence, need for operative revision, infection, and hematoma.

Results: There were 82 same-site recurrences of pressure ulcers after flap surgery (36%) of 232 operations performed in 139 patients. Additionally, 35 flaps (15%) had dehiscences significant enough to necessitate return to the operating room for revision. Using multivariate regression analysis, several variables were found to be significantly associated with the recurrence of pressure ulcers after flap coverage (Table).

Conclusions: The association of elevated HgA1c levels with recurrence presents a modifiable risk factor that may provide improvement in surgical cure rates. Patients who have undergone previous unsuccessful flap operations make poor candidates for attempted flap coverage, and we propose that operative management should be approached with trepidation if at all, particularly in those patients with ischial ulcers. These factors highlight a population of re-operative ischial ulcers that warrant detailed study of conservative management alternatives and innovation in peri-operative and preventative measures to improve operative success in these particular high-risk patients rather than subjecting patients to endless, wasted flap attempts.

Multivariate Predictors of Recurrence	Odds Ratio	95% CI	Significance (p-value)
Ischial Wound	2.87	(1.35-6.10)	0.006
Any Previous Same Site Failure	3.77	(1.76-8.07)	0.001
Poor Diabetes Control (A1c >6%)	6.90	(1.01-47.53)	0.050

Variables Entered Into The Model: Depression, Previous Flap Surgery, Previous Flap Failure, Age <45 at time of Surgery, Wound Location, Poor Diabetes Control (A1c >6), Fecal Diversion, Mental Status, Albumin < 3.5, Procedure Length

TOPICAL P38 MAPK INHIBITION ATTENUATES BURN WOUND INFLAMMATORY SIGNALING AND REDUCES SYSTEMIC INFLAMMATION AND ACUTE LUNG INJURY: A STUDY OF THE EFFECT OF TIMING OF APPLICATION

Carter D, McCue E, Arbabi S

Background: The relationship between local injury or inflammation and subsequent systemic inflammatory response (SIRS) has not been well elucidated in the current literature. In a burn injury model, we have demonstrated the efficacy of topical p38 MAPK inhibition in significant reduction of burn wound inflammatory signaling. Topical post-burn application of p38 MAPK inhibitors reduced expression of inflammatory cytokines and chemokines in the local burn wound. Topical application of p38 MAPK inhibitors reduced pulmonary expression of inflammatory mediators, neutrophil sequestration, microvascular injury, and pulmonary edema. Many potential treatments in the past were effective only if applied before the injury, making them clinically nonviable. In our preliminary experiments, the MAPK inhibitors were topically applied after the injury. However, the time from injury to treatment was short -within minutes after burn injury. In the present study, we seek to determine the effect of delayed application of topical p38 inhibitors to the burn wound. This is an important question as practical use of this product may necessitate a delay in application from time of injury.

Methods: Wild type (C57) mice were used as subjects. Mice were placed into four groups: 1. Sham (SH) 2. Control Burn (CTRL) 3. Burn w/ immediate inhibitor application (SB) 4. Burn w/ inhibitor @ 4hrs (SB4). All groups except sham underwent a 40% TBSA partial thickness hot water scald burn procedure. The sham group had a simulated burn with room temperature water. All groups had vehicle or vehicle + inhibitor applied as specified by group. Further topical applications were applied every 8 hours. Tissues were harvested at 20 hours post burn injury. Skin and lung tissues were prepared and analyzed by ELISA for IL-6, MIP-2, TNF-alpha and IL-1b. RT-PCR was used to further evaluate skin samples for IL-6 cytokine expression. The above experiment was duplicated with the addition of Evan's blue injections prior to tissue harvest. The tissues were analyzed for mcg EB/ mg of tissue as a measure of microvascular injury.

Results: Topical p38 MAPK inhibitor was shown to reduce burn wound cytokine expression in both the time zero and 4 hour application groups when compared with burn controls (CTRL). There was no significant difference between SB and SB4 groups. This effect was demonstrated with respect to IL-6, TNF-alpha and MIP-2 ELISA on burn skin tissue. RT-PCR results were consistent with ELISA results. Topical p38 MAPK reduces pulmonary cytokine expression in both SB and SB4 groups compared to CTRL group. This effect was demonstrated by IL-6 and MIP-2 ELISA of lung tissue. Again, there was no significant difference between SB and SB4 groups. The Evan's Blue study showed reduced levels of tissue EB in lung and skin for both SB and SB4 groups when compared to control.

Conclusion: The effectiveness of topical p38 MAPK inhibitor is retained with delayed application. In this study, we have demonstrated no difference in effect with immediate application versus application at 4 hours. This topical inflammatory inhibitor represents a promising and novel method of combating SIRS secondary to burn injury. The ability to maintain efficacy with delayed application enhances the potential usefulness in "real life" situations where immediate application of the inhibitor would be impractical. Topical "inflammatory source control" would be a useful adjunct to the current standards of burn care with the potential for improved survival due to inhibition of SIRS and related systemic complications.

S1P REGULATES EXPRESSION OF SMOOTH MUSCLE α-ACTIN BY S1P2-MEDIATED ACTIVATION OF RHO AND CALCIUM MOBILIZATION

Grabski AD, Shimizu T, Deou J, Reidy MA, Clowes AW, Daum G

Background: Restenosis is a major complication following surgical interventions to repair occluded arteries and is characterized by narrowing of the vessel lumen. Both negative remodeling and intimal hyperplasia contribute to the development of restenosis with the latter caused by excessive smooth muscle cell (SMC) migration and proliferation. Injury-induced phenotypic modulation of medial SMCs, due to loss of SMC differentiation gene expression, likely contributes to this pathologic injury response, yet the underlying molecular mechanisms controlling this process remain to be identified. SMC differentiation genes are regulated by the transcription factor serum-response factor (SRF), which binds to specific sequences (CArG boxes) in the promoter or enhancer regions of these genes. Interestingly, others have shown that binding of SRF co-factors, which are thought to promote SMC differentiation gene expression, to the CArG boxes depends upon activation of Rho. We have previously shown that sphingosine-1-phosphate receptor 2 (S1P2) null mice, but not their wild-type littermates, form large intimal lesions after arterial injury. Here, we demonstrate that expression of smooth muscle alpha actin (SMA) is markedly decreased after injury in S1P2-null carotid arteries. We present evidence that the S1P2-dependent activation of Rho and release of intracellular calcium are essential for the increase in SMA expression observed in response to sphingosine 1-phosphate (S1P). Our data therefore suggest that sphingosine 1-phosphate receptor 2 (S1P2) might protect against lesion formation by promoting expression of SMC differentiation genes.

Purpose: To identify the S1P2-dependent signaling pathways which promote expression of SMA after arterial injury *in vivo* and following stimulation with S1P *in vitro*.

Methods: Carotid arteries from wild-type and S1P2-null mice were harvested at various timepoints after injury. Total RNA and protein were extracted from arterial lysates and analyzed for expression of SMA by real-time PCR and Western blotting, respectively. For *in vitro* studies, SMCs were prepared from uninjured carotid arteries of wild-type and S1P2-null mice. Total RNA and protein were extracted from quiescent SMCs and after various timepoints of stimulation with S1P and analyzed for SMA expression. To investigate the role for Rho and calcium in SMA expression, SMCs were incubated with pharmacological inhibitors prior to stimulation with S1P. Protein and mRNA were extracted and SMA expression determined. Rho activity was measured using an ELISA-based assay and calcium transients quantified by laser scanning confocal microscopy using a fluorescent calcium indicator dye.

Results: Expression of SMA is decreased at 7 days after carotid ligation injury in S1P2-null arteries but less in wild-type arteries. In wild-type but not S1P2-null carotid SMCs, S1P promotes expression of SMA mRNA and protein as measured by real-time PCR and Western blotting. Further, S1P activates Rho only in wild-type SMCs and the majority of the intracellular calcium transient is S1P2-dependent. Both of these events are required for SMA expression as the Rho inhibitor, C3 exotoxin, the calcium-SERCA pump inhibitor, thapsigargin, and the intracellular calcium chelator, BAPTA-AM prevent S1P-induced SMA expression. Activation of RhoA by S1P does not require calcium, suggesting that at least two independent signaling pathways operate to regulate S1P-induced SMA expression.

Conclusions: We demonstrate that compared to wild-type arteries, S1P2-null arteries express less SMA after injury. Our *in vitro* data suggest that S1P induces expression of SMA in a S1P2-dependent manner. We further show that S1P2 regulates activation of Rho and release of calcium, and that both of these events are required for SMA expression. Taken together, these data are consistent with a role for S1P2 in regulating expression of SMC differentiation genes after injury, and might explain why S1P2-null mice develop large lesions after carotid injury.

OMEPRAZOLE INDUCES CELL DEATH IN GASTRIC GLANDS THROUGH A THIOL OXIDATION PATHWAY.

Kohler J, Blass A, Liu J, Tai K, Soybel D

Introduction: Omeprazole is used to treat many forms of acid peptic disease. Its molecular targets include thiol (S-H) -rich regions in the gastric H^+/K^+ ATPase. Exposure of gastric glands to omeprazole causes cell death. One potential pathway of cell injury is the release of intracellular zinc stores, which we have demonstrated in isolated gastric glands exposed to thiol oxidants. The goals of this study were to determine: first, whether omeprazole-induced cytotoxicity can be demonstrated *in vitro*; second, whether toxicity is due to uncontrolled accumulation of Zn^{2+} in the cytoplasm; and third, whether omeprazole-induced cell death is mediated by thiol oxidation.

Methods: Isolated rabbit gastric glands were incubated with omeprazole (100 μM) for 3 hours. Metal chelators (TPEN and BAPTA) and thiol reducing agents (dithiothretol, DTT) were added in co-incubation. A fluorescent reporter, fluozin-3, was used to monitor cytoplasmic Zn^{2+} and cell viability was measured by monitoring uptake and conversion of calcein-AM.

Results: Omeprazole caused a 38% decrease in gastric gland viability after 3 hours co-incubation ($P < 0.001$), compared to control. Exposure to omeprazole did not increase baseline levels of cytoplasmic Zn^{2+}, and concurrent addition of metal chelators to these cells was not protective. In contrast, concurrent exposure to DTT completely protected cells from injury caused by omeprazole.

Conclusion: Omeprazole induces cell death through a thiol oxidation pathway. This pathway is not dependent on Ca^{2+} or release of Zn^{2+}, and, given its rapid onset of action, may also be independent of its ability to inhibit acid secretion.

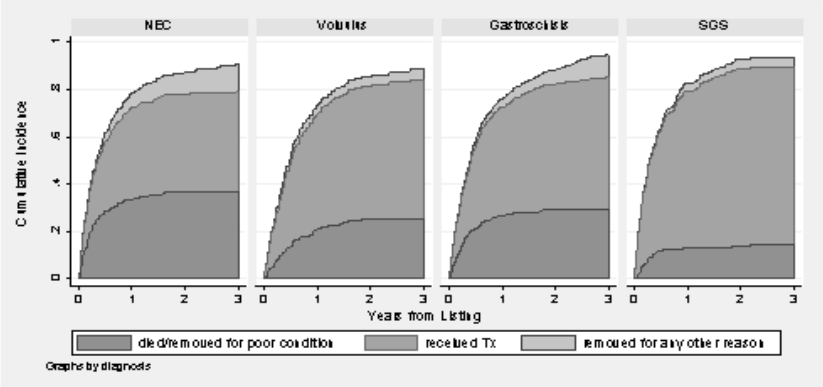
OUTCOMES IN CHILDREN WITH INTESTINAL FAILURE FOLLOWING LISTING FOR INTESTINAL TRANSPLANT

Lao OB, Healey PJ, Perkins JD, Reyes JD, Goldin AB

Purpose: The interval of time from listing to intestinal transplant for specific conditions is unknown. The purpose of this study was to describe the population of pediatric patients waiting for intestinal transplant and to evaluate the risk of death or transplant by specific disease states.

Methods: We studied the United Network for Organ Sharing (UNOS) database (1/1/1991-5/16/08), identified all patients ≤21years-old at first listing for intestinal transplant and examined their age, sex, weight, and diagnoses leading to listing. Time to list removal was summarized with cumulative incidence curves. We performed a multinomial logistic regression analysis to compare relative risk ratios for removal from the list for transplant, death or other reasons.

Results: We identified 1,712 children listed for intestinal transplant (57% male, 51% < 1 yr at listing). Median weight at listing was 8.1kg (IQR 6.1-14.1). The most common conditions for listing were gastroschisis (23%), necrotizing enterocolitis (NEC) (19%), short gut syndrome (13%), and volvulus (12%). Of the 852 patients transplanted, median time to transplant was 114 days (IQR 40-227), with 69% also receiving a liver. Median age and weight at intestinal transplant were 1yr (IQR 1-5) and 10kg (IQR 6.5-16.3). There were 694 children removed from the list. The regression analysis comparing relative risk of removal from the list for transplant versus death demonstrated significant differences among disease conditions ($p < 0.01$). Compared to the gastroschisis group, the relative risk ratio for death versus transplant was higher in the NEC group ($p=0.015$), lower in the short gut syndrome group ($p=0.001$) and not significantly different in the volvulus group ($p=0.97$).



Conclusions: We have described the population of pediatric patients listed for and receiving an intestinal transplant. We conclude that the relative risk of transplant versus death in this population varies significantly by the disease state of the patient.

MORBIDITY AND MORTALITY IN PATIENTS WITH RUPTURED ABDOMINAL AORTIC ANEURYSMS; IMPROVING OUTCOMES WITH A MODIFIED APPROACH

Quiroga E, Tran N, Meissner M, Hatsukami T, Kohler T, Starnes B

Background: Peri-operative mortality after open repair of ruptured abdominal aortic aneurysms (rAAA's) has been quoted to be between 41 and 48% and has not improved significantly in the past two decades. Our institution treats between 30 and 50 patients per year with ruptured aneurysms and our institutional overall mortality during the past five years has averaged 62%. We sought to evaluate the effect of implementation of an algorithm to manage these patients with a preference for endovascular aneurysm repair (EVAR) when feasible.

Methods: Our protocol for managing rAAA's was approved by the Institutional Review Board. Data on patients presenting with rAAA between July 1, 2002 and June 30, 2007 were reviewed and used for comparison to prospectively collected data. Data on patients presenting after July 1, 2007 were collected prospectively on all patients and primary outcome measures were 30-day mortality and overall mortality. Transfusion requirement was compared between those patients undergoing EVAR and those undergoing open repair. Data was analyzed using Chi Square and Fisher's Exact Tests where appropriate.

Results: Between July, 2007 and May, 2008, 31 patients with ruptured aneurysms were managed at our institution. Fifteen patients (48%) underwent successful EVAR and fifteen patients (48%) underwent open repair. One patient underwent comfort care only. Three patients in the EVAR group (20%) and six patients in the open group (40%) died during the follow up period for an overall mortality of 30%. Overall mortality between the two time periods differed significantly, p=0.02. Average transfusion requirement for those undergoing EVAR was 1 unit (0-13) and for those undergoing open repair was 8 units (0-19). The difference in transfusion requirement amongst survivors in each group was not statistically significant (p= 0.06).

Conclusions: Algorithms for the management of ruptured abdominal aortic aneurysms serve as surrogates for an organized approach to managing this disease process and reducing overall mortality. Variables affecting outcome after ruptured aneurysm repair in the age of endovascular treatment remain to be defined.

ENDOLUMINAL TREATMENT OF OBESITY: HOW A NOVEL ENDOSCOPIC SUTURING DEVICE MAY CHANGE THE FACE OF BARIATRIC SURGERY

Soares R, Wright A, Hwang J, Montenovo M, Oelschlager B

Bariatric Surgery is effective in the treatment of obesity and its comorbid conditions, but carries a significant risk. We have developed endolumenal suturing techniques that can expand the endolumenal options for treatment of morbid obesity. We used a novel prototype device – the flexible Endo Stitch™ (Covidien Surgical Devices). This is a flexible suturing device with a suture with unidirectional barbs (V-lock™) that pass through tissue but will not retract back, thus obviating the need for knot-tying. The procedures were developed in a porcine ex-vivo model.

Study #1 (Revision of Gastric Bypass): Weight regain following gastric bypass has been associated with both enlargement of the gastric pouch and with dilation of the gastro-jejunal anastomosis. The first experiment addressed the revision of the pouch and stoma by using endolumenal sutures. We created an 8x8x10cm gastric pouch from porcine gastric explants, then an anatomosis using a 31mm circular stapler. By using the prototype endostitch and endoscopic guidance, we were able to consistently reduce the volume of the pouch and the diameter of the stoma (table1).

	Before Plication	After Plication	% Reduction
Stoma Diameter (mm)	27±2	15±2	40±11
Pouch Volume (ml)	134±83	72±36	40±10

Table 1- Volume of the pouch and diameter of the stoma. (N=10)

Study #2 (DeNovo Endoluminal Gastroplasty): The creation of an endoluminal gastroplasty could be used for treatment of morbid obesity in patients with high surgical risk or the superobese as a first staged procedure. We created an endoluminal vertical gastroplasty, based in the lesser curve, with a calibrated outlet (figure1). In table 2 the dimensions and burst pressures of the endolumenal gastroplasties are shown.

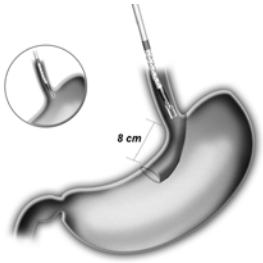


Figure 1

Explant #	Pouch volume	Diameter of the stoma (m	essure (mmHg)
1	18ml	18	
2	12ml	15	67
3	42ml	18	21

Table 2. N=3

Conclusions: Although more animal work needs to be done before the human trials begin, these novel procedures have the potential to reduce the morbidity of weight loss surgery. If effective, this may drastically change the face of bariatric surgery.

GLOBAL SURVEY OF TRAUMA & BURN EDUCATION

Zonies D, Mock C, Civil I, Maier R

Introduction: Injury remains a prominent cause of death and disability among many of the most productive members of society, those between the ages of 1 and 44 years. Over 90% of these deaths occurred in low & middle-income countries. The World Health Organization has recently adopted a resolution to urge strengthening of trauma and emergency care services. In particular, it urged greater work to "ensure that appropriate core competencies are part of the relevant health curricula and to promote continuing education for providers of trauma and emergency care." In many countries, practitioners other than surgical specialists may be the initial provider of care for injured patients.

Purpose: This current survey seeks to investigate global educational activities for trauma and burn care delivered to medical students.

Methods: An internet based survey was developed and distributed to final year medical students through the International Federation of Medical Students Association. The study was conducted from March to November 2008. Demographic variables included age, gender, country and year of training. Questions pertaining to both instruction and specific skills in burn and trauma care were assessed.

Results: There were 1,502 responses from 77 countries (Fig 1). Because 721 respondents (48%) reported being in their pre-clinical or early clinical years, the remaining analysis was restricted to self-reported final year medical students (n=776). There were 394 females (51%) and 377 males (49%).


Figure 1

Over 93% of final year students reported receiving some form of trauma or burn training, with 79% reporting a minimal compulsory requirement. Sixty percent of respondents reported the opportunity to electively participate in a trauma or burn rotation. When stratified by economic region, it was more likely to be available in upper-middle or high-income countries. Among graduating students, 18% planned to establish a general practice, 22% remained undecided, and 60% planned to pursue additional training. However, only 22% of final year students planned to pursue further training in emergency medicine or surgery.

Time spent learning about trauma and burn care varied considerably, with only 22% spending >2 months. Surgical and emergency medical departments were responsible for the majority of didactic and practical training, accounting for 60% and 55% respectively. Residents and attending physicians were responsible for teaching students in 63% and 71% of the cases. Nursing staff provided education in 12% of cases. In the majority of situations, students received some form of didactic training but most did not have an opportunity for practical exposure. When hypothetically asked if they became the sole care provider, there was significant reluctance to perform critical procedures. Over 99% of students agreed that formal trauma training should be included in medical education. Only 55% of final year students felt prepared to provide care for injured victims.

Conclusion: Trauma education and experience varies among medical students in different countries. Although most students feel that trauma & burn education is a critically important component of their training, only half of final year students feel adequately prepared to provide basic trauma or burn care. Burn care received less attention than trauma care in medical education. These data support the mandate to strengthen global trauma and burn medical education.

EARLY ACUTE KIDNEY INJURY IS ASSOCIATED WITH PROGRESSIVE RENAL DYSFUNCTION AND INCREASED MORTALITY IN SEVERELY BURNED ADULTS

Mosier M, Pham T, Klein M, Gibran N, Arnoldo B, Gamelli R, Tompkins R, Herndon D

Introduction: Although transient oliguria and creatinine elevations are commonly observed during acute burn resuscitation, overt acute renal failure is an ominous sign. Until recently, no consensus existed on the definition of acute kidney injury (AKI). The recently developed Risk, Injury, Failure, Loss, and End-stage (RIFLE) classification provides a stringent stratification of AKI severity, but has not been evaluated in burns. We hypothesized that AKI frequently develops early during resuscitation and is associated with poor outcomes in severely burned patients.

Methods: We conducted a retrospective review of patients enrolled in the prospective observational multicenter study "Inflammation and the Host Response to Injury". A RIFLE score was calculated for all patients at 24 hours and throughout hospitalization. Univariate and multivariate analyses were performed to distinguish the impact of early AKI on progressive renal dysfunction, need for renal replacement therapy (RRT), multiple organ dysfunction (MODS), and hospital mortality.

Results: A total of 221 adult burn patients were included. Patients were 73% male with a mean age of 42 ± 16 years, and a mean TBSA of 42 ± 19%. Crystalloid resuscitation averaged 5.2ml/kg/%TBSA, with urine output of 1.0 + 0.6cc/kg/hr at 24 hours, without significant differences between patients with and without AKI. Sixty-two patients met criteria for AKI at 24 hours: 21 patients (10%) classified as Risk, 34 patients (15%) as Injury, and 7 (3%) as Failure (table). After adjusting for age, TBSA and inhalation, early AKI was associated with an adjusted odds ratio of 2.7 for death (95% CI 1.03-6.93, p=0.04).

Conclusions: In this cohort of severely burned patients, 28% of patients developed AKI during acute resuscitation. AKI was not always transient with 26% developing progressive kidney dysfunction. Mortality risk increased with AKI and 75% of patients with early AKI who progressed to RRT did not survive. Better understanding of how early AKI develops and which patients are at risk for progressive renal dysfunction, may lead to improved outcomes.

Category	Early renal function, n (%)	Subsequent renal deterioration, n (%)	Renal replacement therapy, n (%)	Late MODS, n (%)	Mortality, n (%)
No AKI	159 (72%)	46 (29%)	13 (8%)	24 (15%)	21 (13%)
AKI	62 (28%)	16 (26%)	12 (19%)	16 (26%)*	22 (35%)*
Risk	21 (10%)	8 (38%)	5 (24%)	6 (29%)	9 (43%)
Injury	34 (15%)	8 (24%)	7 (21%)	9 (26%)	11 (32%)
Failure	7 (3%)	N/A	0 (0%)	1 (14%)	2 (29%)

* $p<0.05$ compared to "no AKI" patients

ASSOCIATION BETWEEN ADMINISTRATION OF AGED BLOOD AND SEVERITY OF ORGAN FAILURE IN TRAUMA PATIENTS

Hassan M, Warner K, O'Keefe G

Background: Trauma patients frequently receive blood products during the initial resuscitation and surgical intervention phases. Studies have shown that transfused packed red blood cells (pRBCs) has an immunomodulatory effect and influences clinical outcomes.[1-7] It has been suggested that pRBCs stored for longer periods of time further increase the risk of infection and multiple organ failure in trauma patients.[1-7] We conducted this study to determine whether the age of transfused PRBCs influenced the frequency of organ failure and the severity of sepsis in injured patients.

Methods: We retrospectively analyzed all trauma patients enrolled in a prospective cohort study at our Level 1 trauma center who were given at least one unit of packed red blood cells. Sepsis, complicated sepsis and/or organ failure were compared among groups using univariate and multivariate statistical methods. Kaplan-Meier and Cox regression analyses were performed to evaluate potential independent associations of pRBC age on survival.

Results: From June 2003 to June 2007, 1900 trauma patients were prospectively enrolled, of which 835 received any pRBCs within 24 hours of admission. Sixty-eight percent were males (566 patients) and the median age was 40 yrs (IQR 24-52) for the entire study group. Median injury severity score was 26 (IQR 17-34). Median ICU and hospital length of stay was 7 days (IQR 3-14) and 16 days (IQR 9-25), respectively. Two hundred sixty one patients (31%) received 1-2 units of pRBCs, 96 patients (12%) received 3 units, 274 patients (33%) received 4-7 units and 204 patients (24%) received greater than 8 units within the first 24 hours. The median age of blood administered during the initial 24 hours of admission was 18 days (IQR 12-24). During early admission, 66% of patients (n=552) met criteria for multiple organ failure as defined by modified Marshall score[16] $\geq$ 6 and 93% of those patients (n=189) had received $\geq$ 8 units of pRBCs. Of the 261 patients who received 1-2 pRBC units, 11 patients (4%) developed sepsis, mean age of transfused pRBC was 21±10 vs. 19±11 days p=0.613 and 52 patients (19.9%) developed complicated sepsis, mean age of transfused pRBC units 21±12 vs. 19±10 days, p=0.322. Ninety six patients received 3 units of pRBCs and of those patients 4 developed sepsis and 25 complicated sepsis. Mean age of transfused blood in this cohort was 21±6 vs. 19±9 days, p=0.641 and 20±9 vs. 19±9 days, p=0.505, respectively. Of the 247 patients who received between 4-7 units of pRBC's, 23(8%) vs. 79 (29%) developed sepsis and complicated sepsis, respectively. Mean age of transfused blood for this cohort was 18±10 vs. 19±8 days and 19±9 vs. 18±8 days, respectively. Further subanalysis of patients who received $\geq$ 8 units revealed the same trends but again was not statistically significant, 20 ± 8 vs. 17 ± 6 (days), p=0.964.

Conclusion: The risk for sepsis and organ failure in trauma patients transfused pRBCs in the first 24 hours is high. In our cohort, patient age, severity of anatomic injury, signs of shock and the amount of pRBCs transfused are the main determinants of sepsis and organ failure. In the context of these other risk factors, longer duration of pRBC storage does not increase the risk of sepsis, organ failure or death after traumatic injury.

RECOMBINANT ACTIVATED FACTOR VII IN TRAUMA

Hamlat C, Warner K, Jurkovich G

Background: Hemorrhage is the leading cause of early in-hospital deaths due to trauma. Severe, acquired coagulopathy is commonly a component of traumatic bleeding. The use of recombinant activated factor VII (rFVIIa), a drug approved by the FDA for the treatment of bleeding in patients with hemophilia and clotting factor inhibitors, has become increasingly popular in trauma care as an adjuvant to both surgical and non-surgical attempts at control of bleeding. However, it is an expensive therapy ($5,300 per dose) supported only by case series, retrospective reports and a single prospective randomized control trial that failed to show survival benefit. The proper indications, expected outcomes, and risks for this off-label usage remain uncertain.

A previous investigation of rFVIIa at our level one trauma center demonstrated that 91% of patients had not met pre-defined criteria for rFVIIa administration; consequently they suffered a 62% mortality compared to 29% for those who met baseline criteria. Institution guidelines and restriction on the use of rFVIIa were subsequently developed and instituted.

Purpose: To identify and describe the patient population receiving rFVIIa, along with the indications, outcomes and effect of institutional guidelines on the administration of rFVIIa.

Methods: A retrospective chart review was performed on 163 trauma patients who received rFVIIa between 7/2003 and 7/2007. Data collected include demographics, mechanism of injury, ISS, laboratory and physiologic values both pre- and post-rFVIIa administration, rationale, prescriber, location, dosage, procedures performed, quantity of blood products transfused, survival to hospital discharge, and complications. Our guidelines for rFVIIa administration are non-surgical bleeding in a patient with pH> 7.1, fibrinogen> 100 mg/dL, Platelets >75,000 and INR <2.0.

Results: 78 patients received rFVIIa prior to institution guidelines (Early group), and 85 after (late Group). Demographics and ISS between the two groups were similar. In the early group 91% of patients did not meet baseline criteria for rFVIIa administration, compared to 61% in the late group. Overall mortality improved from 59% to 45%, with a clear discrepancy in mortality between those who met (37%) and those did not meet (63%) baseline criteria.

Conclusions: Development and promotion of institutional guidelines for the off-label use of rFVIIa in trauma patients has improved the proportion of patients receiving the drug who meet criteria for its administration and who will most likely benefit from it. However, a majority of patients receiving rFVIIa still did not meet institutional criteria for its use. There is a continued need for provider education and additional systems-based practices to direct its administration.

MORTALITY AND INJURY PATTERNS ASSOCIATED WITH ROOF CRUSH IN ROLLOVER CRASHES

Mandell S, Kaufman R, Mack C, Bulger E

Background: In the United States, a significant number of spine injuries, traumatic brain injuries (TBI), and deaths result from rollover motor vehicle crashes each year though, they make up a small percentage of total crashes. Whether injury is associated with roof crush or the occupant diving toward the vehicles roof remains controversial. There have been no changes in crashworthiness standards for roof strength since 1971. We sought to determine if roof crush is associated with increased mortality, TBI, and spine injury in rollover crashes.

Methods: We searched the NASS CDS database for belted, adult (≥16), non-middle seat passengers involved in rollovers from 1996-2008. We also searched the CIREN database for illustrative cases. Odds ratios (OR) were calculated for mortality, severe injury (AIS ≥3) to the spine, spinal cord, and head for different levels of roof crush. We evaluated the OR for unadjusted data then adjusted for age, gender, and location in the vehicle. A conditional model that accounted for body type, number of quarter turns, curb weight, and rollover as the primary crash event was also used.

Results: CIREN cases demonstrate front seat occupants in the same vehicle where one occupant was subjected to roof crush and the other was not. In each case, the occupant experiencing roof crush had significant injury. NASS CDS data show the risk of mortality, TBI, and spine injury all increased as the rate of roof crush increased. For mortality increased risk occurred at >15cm [15-30cm: OR 2.089 (CI: 1.461-2.987); >30cm: OR 6.301 (CI: 4.369 – 9.087)]. For TBI, increased risk was seen above 15cm crush [15-30cm: OR 1.52 (CI: 1.045-2.21); >30cm: OR 3.672 (CI: 2.456 – 5.490)]. For spine injury increased risk was seen above 8cm crush [8-15cm: OR 1.968 (CI 1.273-3.043); 15-30cm: OR 2.530 (CI 1.634-3.917); ≥ 30cm OR 2.682 (CI 1.474, 4.877). Results were similar across the different statistical models.

Conclusion: There is an association between the amount of roof crush and mortality, spine injury, and TBI. Crash testing has demonstrated that stronger roof strengths can prevent roof crush during a rollover. Adopting higher standards of roof strength to decrease intrusion may decrease mortality and severe injury in rollover collisions.

SIGNIFICANCE OF DISCHARGE TO SKILLED CARE FOLLOWING ABDOMINOPELVIC SURGERY IN OLDER ADULTS

Massarweh N, Legner V, Symons R, McCormick W, Flum D

Introduction: Older adults frequently undergo abdominopelvic surgical operations, yet the risk and significance of postoperative discharge disposition has not been well characterized. We evaluated the population-level risk of discharge to institutional care facilities and its impact on survival among older patients undergoing common abdominopelvic surgical procedures.

Methods: A retrospective, population-based cohort study, using the Washington State hospital discharge database, for 89,405 adults aged 65 and older who underwent common abdominopelvic procedures (cholecystectomy, colectomy, hysterectomy/oophorectomy, and prostatectomy) between 1987 and 2004. Outcomes of interest included discharge location and short- and long-term mortality. Trends were assessed using a nonparametric trend analysis across ordered groups. A Mantel-Haenszel estimator was used to determine the common odds ratio for stratified data. Multivariate logistic regression models were created to evaluate the odds of discharge to institutional care post-operatively.

Results: Advancing age was associated with discharge to an institutional care facility (ICF) following surgery (65-69, [3.3%]; 70-74, [5.7%]; 75-79, [10.8%]; 80-84, [20.6%]; 85-89, [31.8%]; 90+, [43.9%]; trend test, p-value <0.001). Postoperative complications were also associated with discharge to an ICF (21.9% vs. 8.9%, p-value <0.001). Patients discharged to an ICF following surgery had higher 30 day (4.3% vs. 0.4%), 90 day (12.6% vs. 1.4%), and one year mortality (22.2% vs. 5.9%) compared to those discharged home with self-care (p-values <0.001). Compared to similarly aged adults discharged home, patients discharged to an ICF had 4 times higher one-year mortality (Odds ratio 3.9; 95% Confidence interval 3.6 to 4.2). Of those who died following discharge to an ICF, the majority died either at the ICF (53.7%) or on a subsequent hospital admission (31.0%).

Conclusions: Advancing age is associated with risk of discharge to an ICF following abdominopelvic operations. Patients discharged to an ICF are much more likely to die within the first postoperative year and ICF disposition should be considered either a marker of debility and/or a component of patient decline. These findings may be helpful when counseling patients regarding the expected outcomes of ICF placement following surgical intervention.

SURGEON SPECIALTY AND LONG-TERM SURVIVAL FOLLOWING PULMONARY RESECTION FOR LUNG CANCER

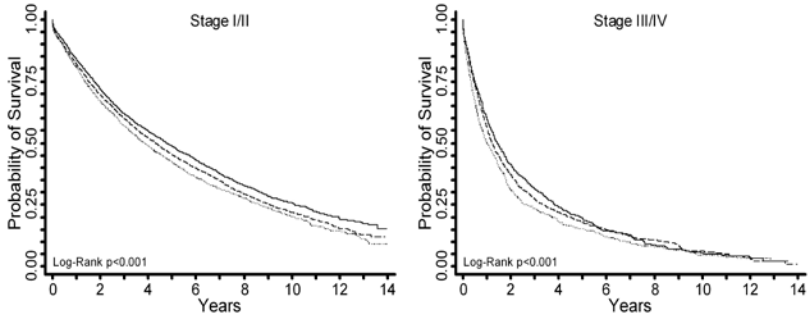
Farjah F, Flum D, Varghese T, Symons R, Wood D

Background: Patients with operable lung cancer may experience better long-term outcomes when treated by surgeons who specialize in general thoracic surgery. An association between surgeon specialty and long-term survival has not been described.

Methods: A cohort study (1992-2002, follow-up through 2005) was conducted using Surveillance, Epidemiology, and End-Results-Medicare data that were linked to the American Board of Thoracic Surgery Diplomates List. Board-certified thoracic surgeons were designated as cardiothoracic surgeons (CTS) if they performed cardiac procedures and as general thoracic surgeons (GTS) if they did not.

Results: Among 19745 patients, 4677 (24%) were cared for by surgeons who were not board-certified in thoracic surgery (NBTS), 8807 (45%) by CTS, and 6261 (32%) by GTS. Of the 1848 surgeons, 770 (42%) were NBTS, 687 (37%) were CTS, and 391 (21%) were GTS. Patient age, comorbidity index, and resection type did not vary by surgeon specialty (all p>0.10). Unadjusted stage-based survival rates did vary by surgeon specialty (Figure 1). After adjustment for patient, disease, and management characteristics, hospital teaching status, and surgeon and hospital volume, patients treated by GTS had an 11% lower hazard of death compared to those who underwent resection by NBTS (HR 0.89, 99% CI 0.82-0.97). The risks of death did not vary significantly between CTS and NBTS (HR 0.94, 99% CI 0.88-1.01) or GTS and CTS (HR 0.94, 99% CI 0.87-1.03).

Conclusion: Lung cancer patients treated by general thoracic surgeons had better long-term outcomes than those treated by surgeons without board-certification in thoracic surgery. These findings have important implications for regionalization of care, pay-for-performance in lung cancer care, and education of an adequate workforce in general thoracic surgery.



General thoracic surgeons (solid line)
Cardiothoracic surgeons (dash)
Not board-certified in thoracic surgery (dot)