The department provides opportunities for scientific research in a wide variety of fields in a warm, friendly and collegial atmosphere. Three separate research groups with international repute provide excellent opportunities for advancement in both basic science and clinical research. Researchers and students have easy access to supervisors and support and close supervision at all times. Modern facilities and easy access to transport ensure a pleasant working environment.

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At Johnson & Johnson medical, surgical training and medical education has always been an integral part of our commitment to transforming patient care and the advancement of minimally invasive surgery. We have facilitated the training of surgeons, operating room nurses and other health care professionals on the latest surgical procedures and instrumentation for decades. We believe in grass roots activity and will continue to support training programs long into the future.
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Research is to see what everybody else has seen, and to think what nobody else has thought.

- Albert Szent-Gyorgyi
The Austin Surgery Research Prize

The Austin Surgery Research Prize was inaugurated in 2003 and supported by Johnson and Johnson Pty Ltd. The main aim of the prize was to foster interest in clinical and basic science research amongst trainees at all levels within the Division of Surgery and reward excellence in achievement. It is gratifying to note that interest amongst trainees has remained high as seen by the number of high quality presentations submitted this year.

We are grateful to Johnson and Johnson Pty Ltd who have remained steadfast in their commitment to supporting research at the Austin. In addition we are also indebted to the senior medical staff of the Austin who have encouraged research amongst the trainees. Without this support much of the work presented here would not be possible.

Prof C Christophi
Head, Department of Surgery
Austin Health
07.30 - 0830 Weekly Surgical Audit

0830 - 0930 Maintaining Quality in Surgery - Prof R Padbury

0930 - 1200 Austin Surgery Research Prize

0930 Liam Kavanagh - “Nurse-led surveillance flexible cystoscopy: evidence of oncological safety.”

0945 Emily Chen - “Mortality trends of Penile Cancer: A prospective whole of population study.”

1000 Dermot O’Kane - “Zinc protects the kidney against warm ischaemia reperfusion injury in a pre-clinical large animal model.”

1015 Daniel Ng Ying Kin - “Nurse-led outpatient clinics are a safe and effective option for the surveillance of low risk postoperative colorectal cancer patients.”


1115 Hui Quing Lee - “Liver Transplantation for Hepatocellular Carcinoma: Inflammatory Markers Predict Recurrence-Free and Overall Survival”

1130 Su Kah Goh - “Circulating DNA: an approach to monitor organ rejection after liver transplantation.”

1145 Adjudication

1200 Announcement of winner & presentation of Prize

If we knew what we were doing it wouldn’t be research.

- Albert Einstein
Nurse-led surveillance flexible cystoscopy: Evidence of oncological safety

Liam Kavanagh1,2, Paul McGivern1,2, Munad Khan1, Rustom Manecksha1,3, Greg Jack1,4, Nathan Lawrentschuk1,2, Damien Bolton1,2, Shomik Sengupta1,2

1 Dept of Urology, Austin Hospital, Melbourne, Australia; 2 Dept of Surgery, University of Melbourne, Melbourne, Australia; 3 Dept of Urology, St. James’s Hospital, Dublin, Ireland; 4 Dept of Urology, UCLA, Los Angeles, USA

Background: Urothelial carcinoma (UC) of the bladder recurs locally, necessitating ongoing surveillance, often by means of flexible cystoscopy (FC). Nurse-led FC services have been introduced in recent years to meet increasing clinical needs. The aim of this study was to assess pick-up rates of recurrent UC at nurse-led FC.

Methods: From September 2012 until July 2015 628 nurse-led FCs at Austin hospital were retrospectively analysed. The endpoints assessed were rates of referral for transurethral resection (TUR) and true diagnosis of recurrent UC, with comparison, using Chi-square analysis, to FC carried out by the nurse endoscopist under supervision during training.

Results: Referral for TUR was made in 84 (13.4%) cases, compared to 32 (17.6%) of 182 during supervised training (p=0.15). Tumour recurrence was confirmed endoscopically or histologically in 61 (72.6%) cases, compared to 19 (59.4%) under supervision (p=0.17). There were no discernible trends over time in referrals for TUR or diagnosis of recurrences when comparing successive 6-month blocks.

Conclusion: Nurse-led FC leads to comparable rates of referral for TUR and diagnosis of recurrent UC, suggesting it is a safe mechanism for surveillance of UC.

PERSONAL CONTRIBUTION

Planning/conceptualization: 60 %
Laboratory work/data collection: 80 %
Data analysis/discussion: 70 %

Liam Kavanagh
Current Position: Urology SET3 Registrar
Dr Liam Kavanagh is currently a SET3 Urology registrar at the Austin hospital. Liam previously completed a Master’s of Surgery degree through the Austin and The University of Melbourne researching Prostate cancer Genomics. Prior to completing his Medical degree at The University of Melbourne, he completed a Bachelor of Pharmacy at Monash University.
Mortality trends of Penile Cancer:
A prospective whole of population study

Emily C Chen¹, Nathan Papa¹, Damien Bolton¹,² and Nathan Lawrentschuk¹,²,³
¹ University of Melbourne, Department of Surgery, Urology Unit, Austin Hospital
² Olivia Newton-John Cancer Research Institute Austin Hospital
³ Peter MacCallum Cancer Centre, Division of Cancer Surgery

BACKGROUND: Penile cancer is a rare urologic malignancy. In western populations the incidence ranges from 0.45-1.7 per 100,000 men in North America, Europe and Australia. Being a rare disease, there has been a paucity of good-quality studies available to base best clinical practice with the majority being single center series. We herein present the first whole of population study to review the mortality trends of penile squamous cell carcinoma.

METHODS: The Victoria Cancer Council registry (VCR) was used to report the cancer-specific survival based on tumor classification and histological grade over the past 15 years. We have identified 251 patients who underwent surgery for penile cancer from 1st January 1998 to 1st December 2013. Kaplan-Meier methods were used to determine survival probability.

RESULTS: The five-year disease specific Kaplan-Meier survival estimate for well differentiated cancer was 87% (95% CI: 73% - 94%), for moderately differentiated cancer 76% (63% - 85%) and for poorly differentiated cancer 52% (40% - 63%). The corresponding five-year estimates for T1 stage cancer were 89% (81% - 94%), 53% (40% - 65%) for T2 disease and 23% (8% - 41%) for T3/T4 stage cancer.

CONCLUSIONS: The five-year disease specific Kaplan-Meier survival estimate for well differentiated cancer was 87% (95% CI: 73% - 94%), for moderately differentiated cancer 76% (63% - 85%) and for poorly differentiated cancer 52% (40% - 63%). The corresponding five-year estimates for T1 stage cancer were 89% (81% - 94%), 53% (40% - 65%) for T2 disease and 23% (8% - 41%) for T3/T4 stage cancer.

PERSONAL CONTRIBUTION

| Planning/conceptualization | 80% |
| Laboratory work/data collection | 100% |
| Data analysis/discussion | 70% |

Emily Chen
Current Position: Non-SET General Surgical Registrar
Currently enrolled in the Master of Surgery degree at The University of Melbourne with the working thesis: ‘The surgical management of penile cancer, an Australian series’.
**Zinc protects the kidney against warm ischaemia reperfusion injury in a pre-clinical large animal model**

O’Kane D\(^1\,^2\), Bolton D\(^1\,^2\), Baldwin G\(^1\), Shulkes A\(^1\), Patel O\(^1\), Ischia J\(^1\,^2\).

**Department of Anaesthesia, Austin Hospital, Melbourne**

**BACKGROUND:** Surgery offers the only definitive cure for renal cancer. Partial nephrectomy (PN) is the gold standard surgical approach for many of these cancers. During these surgeries it is necessary to interrupt the renal blood supply in order to facilitate safe tumour resection, and avoid excessive blood loss. This interruption to renal blood supply, achieved by clamping the renal artery, results in kidney damage depending on the “ischaemia time”. To date there has been no definitive method of preventing or reducing this renal damage in humans. An agent or method that could facilitate protection against ischaemia of this nature would have major implications for long term outcomes of patients undergoing PN, as well as kidney transplant. Our laboratory has previously shown that zinc protects against ischaemia-reperfusion (I-R) injury in a rat model. Rodents are not always reliable as a preclinical model for human disease however, and therefore in this study the renoprotective effect of zinc preconditioning was investigated in a large animal (ovine) model of renal I-R injury.

**METHODS:** Merino ewes were subjected to 60 minutes of occlusion of the left renal artery to induce I-R injury, followed by right nephrectomy. Sheep were preconditioned with intravenous infusion of either zinc chloride (ZnCl\(_2\)) or saline at 24hr and 4hr prior to occlusion. Blood samples were collected daily following surgery for seven days. Serum urea and creatinine concentrations were used as markers of renal function.

**RESULTS:** ZnCl\(_2\) treatment was well tolerated with no obvious adverse effects. The sheep treated with ZnCl\(_2\) (0.5mg/kg) had a marked reduction in renal injury; evidenced by smaller rise in serum creatinine and urea levels after surgery compared with the control sheep. The mean serum creatinine on day 3 for ZnCl\(_2\) treated sheep was 154±9μmol/L as compared to 666±149μmol/L in saline treated sheep (Fig.1). The mean serum urea on day 3 for ZnCl\(_2\) treated sheep was only 6.4±1.3 mmol/L as compared to 34.0±9.6 mmol/L in saline treated sheep.

**CONCLUSIONS:** We have demonstrated that zinc preconditioning protects against warm renal ischaemia in a pre-human (ovine) model. This result has lead to collaboration with a commercial partner, Phebra, to perform phase 1 and 2 human trials of zinc preconditioning in patients undergoing partial nephrectomy.

**PERSONAL CONTRIBUTION**

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Dermot O’Kane

Current Position: Full time Research Fellow

From Ireland. Studied medicine at University College Cork, Ireland, before moving to Australia. Accepted by the Royal Australasian College of Surgeons to SET urology training, but I deferred clinical training to complete a PhD at The University of Melbourne. Currently working full-time as a research fellow within the Urology unit at the Austin Hospital.
Nurse-led outpatient clinics are a safe and effective option for the surveillance of low risk postoperative colorectal cancer patients

Ng Kwet Vee Daniel Ng Ying Kin
Colorectal Surgical Unit, Launceston General Hospital, Tasmania.

BACKGROUND: Colorectal cancer (CRC) represents a significant health burden. Approximately 15,000 Australians are diagnosed annually with colorectal cancer with about 1,000 under the age of 50. One in 12 people develop colorectal cancer before the age of 85. There are nearly 4,000 deaths annually as a result of Colorectal cancer in Australia, the second most lethal cancer behind lung cancer. Forty percent of stage II or III patients will have a recurrence following initial treatment, most of which occurs in first 3 – 5 years. Follow up of CRC aims to provide earlier detection of recurrence and distant disease through surveillance, thus potentially offering curative resection, collection of outcome data and the opportunity to address nononcological post operative issues, such as bowel, urinary and sexual dysfunction. About 90% of bowel cancer cases can be successfully treated if detected in their early stage. The instruments of follow up vary depending on institutions but mostly involved a combination of blood tests such as estimation of Carcinoembryonic Antigen (CEA), liver function tests (LFT), organ imaging e.g. ultrasound of liver, computerised tomography of chest and abdomen, PET scans, and colonoscopy A model of nurse-led colorectal clinic was developed at Launceston General Hospital (LGH) in 2007, in an attempt to standardise the follow-up process and free up colorectal surgeons’ clinic slots to reduce waiting time for new patients. At that time there was no literature guideline although, in the same year, an article was published about a similar clinic in Edinburgh, Scotland, examining the efficacy of one such clinic over 12 months of follow up. The study demonstrated high level of patient and clinician satisfaction.

METHODS: All data for this study were extracted from the LGH Colorectal Cancer Surveillance (CRCS) patient data which has been updated by the stomal nurses since the introduction of the nurse-led clinic in 2007. The current study examines the data collected between September 2007 and November 2012 of our colorectal nurse cancer follow up clinic. The Colorectal cancers were staged according to the American Joint Committee on Cancer (AJCC), also known as the TNM system. The patients were referred by the colorectal surgical team. The criteria for entry is a patient who had surgery with curative intent for Stage I or II disease and operated as a public patient at LGH, therefore, all privately insured patients operated in the public sector were excluded. (Continued overleaf)

PERSONAL CONTRIBUTION

| Planning/conceptualization: | 95% |
| Laboratory work/data collection | 50% |
| Data analysis/discussion: | 90% |

Daniel Ng
Current Position: Unaccredited General Surgery Registrar

Daniel Ng, short for Ng Kwet Vee Daniel Ng Ying Kin, is currently an Unaccredited Surgical Registrar at the Austin Health. Despite holding a British passport, I regard myself as a Mauritian. I have done my schooling till secondary school in Mauritius before leaving for Monash University, where I graduated in 2010. I believe my heart lies in General Surgery, with an extra beat for Colorectal Surgery. I am a sports passionate, especially for Soccer, and my blood is red for the Red Devils of Manchester United.
Occasionally, patients with Stage III disease would be referred. Correspondence from the nurse clinic would be reported back to the colorectal surgeons with a copy to the General Practitioners. This gives the surgeons an opportunity to oversee the clinic in an indirect fashion. The clinic shared among three experienced stomal therapy nurses. Other details about each patient were collected in terms of demographics, tumour (location, stage and operation performed), attendance and detection of recurrence or distant metastatic disease. A survey was randomly performed at the 1 year mark to assess the patient’s understanding of the nurse-led clinic. The experienced stomal nurse would be allocated a weekly outpatient clinic where they would spend the 30 minutes slot to take a history, perform an examination including a per-rectal examination and review of latest results before ordering further tests as per LGH surveillance protocol.

RESULTS: A total of 72 patients were referred to the nurse-led clinic within the 5 year period. There were 11 patients who were operated before September 2007 and initially followed-up by the Colorectal surgical team before referring to the nurse-led clinic upon its introduction. The age group spread from 36 to 84 years old, with an average age of 66.6 years old. The were more males (42) than females (30), with the males being slightly older on average (66.7 v/s 66.3). The majority of cancers resected were in the rectum (N=22, 31%) and sigmoid (N=12, 17%), comprising of nearly half of the cohort and Caecum (N=7, 10%), ascending colon (N=9, 13%) and hepatic flexure (N=5, 7%) to contribute to the group of right sided colonic cancer. Therefore, the most common procedures performed were an anterior resection (42%) and a right hemicolectomy (42%). The cancers were staged post operatively by combining pathological examination of the tumour and CT scan of the chest, abdomen and pelvis. There were 4 stage 0, 30 stage I, 33 stage II and 5 stage III. All the 5 stage III patients successfully completed the nurse-led surveillance program.

Of the 72 that were referred to the nurse-led surveillance clinic, 12 patients are still currently undergoing surveillance at the time of writing the article. Therefore, 31 patients have successfully completed the 5 year surveillance program, 15 were transferred back to their General practitioner (geographical convenience), 9 transferred back to the colorectal surgical team, 3 died and the remaining 2 patients were discharged (Loss to follow-up, migrated overseas). Amongst the 3 patients that passed away, 2 were not colorectal cancer related (New lung primary cancer and respiratory failure secondary to chronic obstructive airways disease) and the cause of death of the other patient remains unknown (all records destroyed). Amongst the 9 patients transferred back to the Colorectal Surgical team, 2 were found to have a recurrence of disease in terms of a metachronous cancer and a lung metastatic disease, while 1 case was loss to follow up as the records were destroyed. Assuming the worse outcome scenario for the sake of the study that the case destroyed was not a recurrence, the pick-up rate from the nurse-led clinic would be 22.2% (2/9). The survey Questionnaires were distributed randomly to patients. A total of 24 were given and 17 were completed, making a response rate of 71%. The survey indicated that 82% of the patients received answers that they could understand “All of the time” and the remaining 18% understood the answers “most of the time”. Moreover, 94% of the responses reported “excellent” care, while the remaining 6% reported the care as “good”. A total of 481 clinic sessions with the stomal nurse occurred since September 2007. Given that each appointment was 30 minutes’ duration, a total of 240.5 hours were saved by the surgical team.

CONCLUSION: This study comprises of a small cohort of patients but it gives an overview of the safety of the nurse-led clinic for surveillance of low risk post-operative colorectal cancer patients. The patients are generally satisfied and feel safe with the service. There are not many similar articles to compare with in Australia and none in the state of Tasmania thus far. Five patients with stage III disease completed successfully the colorectal surveillance program proving that there is a potential to extrapolate this service to stage III and even stage IV disease. With the aid of further studies, a more established and targeted guideline can be created in the hope to making nurse-led colorectal cancer surveillance a mainstay in every colorectal surgical unit.

Hughes K, Neoh D
Plastic & Reconstructive Surgery Unit, Austin Health

BACKGROUND: Implant-based reconstruction is the most common type of reconstruction of the breast post mastectomy, however it is not without its limitations. The use of acellular dermal matrix (ADM) as an inferolateral hammock to cover and support the inferior pole of the implant has many advantages. The practice of breast reconstruction using ADM has been gaining momentum internationally for several years, however access has only become easily available in Australia with the introduction of Flex HD (a human ADM allograft) this year. We present a single surgeons experience using Flex HD for immediate breast reconstruction, to our knowledge the first Australia series.

METHODS: Retrospective case series of a singles surgeons first 20 patients undergoing immediate breast reconstruction using Flex HD.

RESULTS: A total of 20 patients (30 breast reconstructions) were included in the study. The average age of patient was 47 (33-68), with an average body mass index of 21 (18-27), and mostly non-smokers (75%). 21 (70%) cases were for cancer treatment and 9 (30%) were prophylactic. There were 15 (75%) two staged expander based reconstructions, and in 5 patients (25%) we were able to use a direct to implant single staged reconstruction. The use of Flex HD allowed higher than normal intra-operative expander filling volumes, on average 61% of expander capacity (32-100), which meant fewer post operative expander fills (1.9) and decreased time to second stage. Complications included seroma (23%), infection (6%), nipple necrosis (15%), threatened implant (3%), wound healing (3%) and “red breast” (3%). There were no cases of implant loss.

CONCLUSIONS: Flex HD is a useful adjunct in the immediate implant based reconstruction that improves cosmetic outcome and provides potential cost saving benefits. However, it can be associated with slightly increased risk so it’s use should be rationalised especially in at risk populations.

PERSONAL CONTRIBUTION

| Planning/conceptualization: | 90% |
| Laboratory work/data collection | 100% |
| Data analysis/discussion: | 100% |

Kimberley Hughes
Current Position: Unaccredited Plastic Surgery Registrar
Kim graduated from the University of Tasmania and completed her internship and residency year in Launceston before moving to the Austin for HMO3 to pursue a career in Plastic Surgery.
Zinc preconditioning protects against renal ischaemia reperfusion injury: In-vitro model and mechanisms

Luke Gibson¹², Damien M Bolton¹², Graham Baldwin¹, Arthur Shulkes¹, Joseph Ischia¹², Oneel Patel¹

¹ Department of Surgery, University of Melbourne ² Department of Urology, Austin Hospital.

BACKGROUND: Partial nephrectomy (PN), when compared with total (radical) nephrectomy, preserves renal parenchyma to maintain renal function, improves overall survival and significantly decreases the risk of chronic kidney disease, however, the peril of ischaemia-reperfusion injury (IRI) means that less than 25% of renal cancers are treated by PN, despite the majority of cases being suitable. Currently there are no techniques or drugs for protecting the human kidney against IRI in clinical use. Zinc (Zn) is an essential nutrient, with a multiplicity of biological roles in cell proliferation, differentiation, growth, genomic stability and energy metabolism. Novel unpublished findings from our laboratory have demonstrated a protective effect of zinc pretreatment against renal IRI in a rat model. This study aims to explore the in-vitro mechanisms by which zinc preconditioning protects against renal IRI.

METHODS: Immortalized human kidney cells (HK-2) were used. Pharmacokinetics of zinc uptake were measured using Fluozin 3 probe and fluorescence spectroscopy. Induction of hypoxia-inducible transcription factors (HIFs), key proteins in a cell’s ability to adapt to hypoxia, was measured using western blot technique. The effect of Zn treatment on cell survival was assessed in three ways; using an oxygen/glucose deprivation (OGD) renal ischemia model, serum starvation over an extended period and by simulating free radical damage by the addition of hydrogen peroxide (H2O2) to cell samples. Survival was compared with other potent HIF stimulators cobalt and prolyl-hydroxylase inhibitor FG-4592. Intermediates of cellular metabolism were studied using gas chromatography mass spectrometry (GC-MS) with the assistance of Metabolomics Australia.

RESULTS: Free intracellular zinc in HK-2 cells increased to 13.4±0.45 nM following 4 hour treatment with 50µM ZnCl₂, compared to 3.8±0.3 nM in untreated control cells. Zinc significantly increased expression of HIF1α and HIF2α, however less so than cobalt and FG-4592. Cell survival in OGD model was increased by 219±12% in oxygen deprived HK-2 cells pretreated with 50µM ZnCl₂, significantly more so than cobalt or FG-4592 pretreated cells. Zinc pretreatment also conferred a survival advantage in H2O2 and serum starvation models. Metabolomic assessment revealed a significant change in 35 intermediates of metabolism in zinc treated cells when compared with control, most notably, tricarboxylic acid (TCA) cycle intermediates succinate, fumarate and malate.

CONCLUSIONS: Pretreating immortalized human kidney cells with zinc chloride improves cell survival in cellular models of renal IRI, which is independent of zinc’s stimulatory effects on HIFs. Significant changes in cellular metabolism, particularly within the TCA cycle, may be a mechanism by which free radical generation and damage is prevented.

Luke Gibson
Current Position: Masters of Surgery student (full time research)

Luke graduated from Monash University in 2010, after which he completed internship and surgical resident years at the Austin, gaining an interest in urology. He has since been enrolled in a Masters of Surgery degree consisting of full time research with the Departments of Surgery and Urology.

PERSONAL CONTRIBUTION

Planning/conceptualization: 33%
Laboratory work/data collection 80%
Data analysis/discussion: 50%
eHarmony for Livers: A Method for Donor-Recipient Matching in Liver Transplantation

Lawrence Lau1; Yamuna Kankanige2, James Bailey2, Benjamin Rubinstein2, Robert Jones1, Michael Fink1, Graham Starkey1, Bao-Zhong Wang1, Christopher Christophi1, Vijayaragavan Muralidharan1

1 HPB & Transplant Unit, Department of Surgery, Austin Health, University of Melbourne, Melbourne, Australia; 2 Department of Computing and Information Systems, University of Melbourne, Melbourne, Australia

BACKGROUND: Organ allocation for liver transplantation is a delicate balance between the utility of a limited resource and the risk of harming a recipient with an unsuitable organ. The conventional Donor Risk Index (DRI) fails to account for complex, non-linear relationships between multiple prognostic factors and does not consider factors which are specific in the setting of an Australian transplant unit. Artificial intelligence using machine learning algorithms can detect complex interdependencies in large volumes of data and can create predictive models specific to the population from which the data set was derived.

METHODS: The Victorian Liver Transplant Unit database containing a comprehensive dataset of all transplants between 2010 to 2013 were included in the study. Training and testing datasets were constructed by bootstrap sampling with replacement 1000-fold. After considering all available donor, recipient and transplant factors (282 in total), the top 15 factors that influence the outcome of graft failure within 30 days, were selected using Random Forest characteristic ranking method. An index to predict the outcome of interest was developed using those factors.

RESULTS: Donor Risk Index (DRI) predicts graft failure within 30 days with an area under the receiver operating characteristic curve (AUC-ROC) value of 0.680 (95% CI 0.669-0.690), while an index using the same factors as DRI, which is trained for the Australian context achieves an AUC-ROC of 0.697 (95% CI 0.688-0.705). The combination of the factors used in DRI with the model for end-stage liver disease (MELD) score yields an AUC-ROC of 0.764 (95% CI 0.756 – 0.771). Using the top 15 donor and recipient characteristics results in an AUC-ROC of 0.816 (95% CI 0.810- 0.822).

CONCLUSIONS: Computer-based algorithms based on ANN are powerful tools that can accurately predict outcome following liver transplantation which is specific to The Victorian Liver Transplant Unit. Accurate outcome prediction may be useful during donor organ assessment to potentially allow for optimized donor-recipient matching.

PERSONAL CONTRIBUTION

| Planning/conceptualization: | 100% |
| Laboratory work/data collection | 100% |
| Data analysis/discussion: | 80% |

Lawrence Lau

Current Position: General Surgical Registrar (SET5), fulltime clinical
Lawrence is a passionate surgical registrar who has made it his raison d’être to help donor livers find and connect with their perfect match.
Liver Transplantation for Hepatocellular Carcinoma: Inflammatory Markers Predict Recurrence-Free and Overall Survival

Hui Quing Lee, Su Kah Goh, Robert Jones, Chris Christophi, Vijayaragavan Muralidharan. HPB & Transplant Unit, Department of Surgery, Austin Health, University of Melbourne, Melbourne, Australia;

BACKGROUND: Tumour recurrence (12 - 19%) and mortality (19 – 40%) is a significant challenge after orthotopic liver transplant (OLT) for hepatocellular carcinoma (HCC). Adopting prognostic methods such as Milan criteria have led to improved outcome. Recent studies have indicated an increased risk of tumour recurrence and death in patients with elevated inflammatory markers such as neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR). These findings have not been demonstrated in an Australian-based population. Therefore, we conducted a retrospective analysis of OLT for HCC to establish the predictors of recurrence-free survival (RFS) and overall survival (OS) at five years with specific focus on the markers of inflammation.

METHODS: Records of 155 consecutive patients undergoing liver transplant for HCC from July 2003 to December 2014 were obtained from the Liver Transplant Database. Clinico-pathological data were analysed to determine the predictors of RFS and OS. Raised NLR is defined as NLR ≥ 5 and raised platelet-lymphocyte ratio (PLR) is defined as PLR ≥ 300. Univariate and multivariate analysis were conducted using Kaplan Meier survival analysis and Cox regression analysis.

RESULTS: The median follow-up time was 4.8 years. Median time to recurrence of HCC was 9.3 months. Hepatocellular carcinoma recurred in 18 patients (12%) after liver transplant. Five year overall survival rate was 81% (n = 125). High preoperative NLR was significantly associated with poorer overall survival at 5 years (Figure 1), but no difference in HCC recurrence was observed. NLR ≥ 5 at 6 months post OLT was a predictor for both RFS and OS (p = 0.037; p = 0.049). High preoperative PLR does not predict RFS and OS (0.264; 0.221) but high PLR at six months post OLT increased risk for mortality within 5 years post transplant (p=0.036). Multivariate analysis identified preoperative NLR ≥ 5, maximal tumour diameter ≥ 30mm and longer cold ischemia time as predictors of 5 years overall survival. Microvascular invasion and maximal tumour diameter ≥ 30mm increases the risk of HCC recurrence.

CONCLUSIONS: This is the first Australian-based study that describes preoperative NLR and postoperative NLR and PLR as predictors of HCC recurrence and survival after liver transplantation for HCC. NLR are readily available and this tool can potentially act as a useful adjunct to Milan criteria in selection of liver transplant recipient who may benefit the most in survival after transplant. NLR may also be useful in guiding the frequency of surveillance for recurrence after liver transplant.

PERSONAL CONTRIBUTION

| Planning/conceptualization: | 10% |
| Laboratory work/data collection | 65% |
| Data analysis/discussion: | 80% |

Hui Quing Lee
Current Position: Surgical HMO2, fulltime clinical
Hui is currently a second year surgical resident at the Austin Hospital. She graduated from the University of Melbourne in 2013. She is keen to pursue a career in surgery.
Circulating DNA: an approach to monitor organ rejection after liver transplantation

Su Kah Goh\(^1\), Hongdo Do\(^2\), Vijayaragan Muralidharan\(^1\), Alexander Dobrovic\(^2\) & Chris Christophi\(^1\)

\(^1\) Department of Surgery, University of Melbourne, Austin Health, \(^2\) Translational Genomics and Epigenomics Laboratory, Olivia Newton-John Cancer Research Institute

**BACKGROUND:** Up to twenty percent of patients will develop an episode of rejection in the first twelve months after liver transplantation. Liver biopsy is the gold standard for the diagnosis of organ rejection. However, this procedure is invasive and carries a risk of bleeding and sepsis. Recent studies have proposed the use of donor-specific circulating cell-free DNA (dscfDNA) as a blood-based biomarker for organ rejection. Unlike current methodologies used to quantify dscfDNA, we aimed to develop a rapid and cost-effective approach for serial monitoring of graft health after liver transplantation.

**METHODS:** Five patients undergoing liver transplantation were prospectively recruited. Droplet digital PCR was used to analyze recipient blood samples collected at various timepoints. This PCR platform allows precise quantification of dscfDNA molecules in the circulation of the recipient. The levels of dscfDNA were compared with conventional serum liver biochemistry and clinicopathological factors.

**RESULTS:** Levels of dscfDNA were reflective of graft health. Marked increase in dscfDNA levels were observed in one patient who developed an episode of acute cellular rejection. Cholestasis did not increase the levels of dscfDNA after liver transplantation. Turnaround time for quantification of dscfDNA is attainable under 6 hours.

**CONCLUSIONS:** Our methodology to accurately quantify dscfDNA was feasible and clinically applicable. Furthermore, our preliminary results suggest that this non-invasive biomarker can facilitate timely and serial monitoring of graft health for organ rejection.

**PERSONAL CONTRIBUTION**

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Su Kah Goh

Current Position: SET3 General Surgery Trainee, PhD candidate

Su Kah graduated from the University of Melbourne in 2008. He has completed two years of accredited general surgery training at the Austin Health and is currently undertaking a PhD to study the role of circulating DNA in surgical liver disorders.
AUSTIN RESEARCH PRIZE - PAST WINNERS

2003: Mehrdad Nikfarjam - The Influence of Vascular Inflow Occlusion on Progressive Liver Necrosis and Microvasculature Following Interstitial Laser Thermotherapy


Stephen Warrillow (Joint Winner) - A randomised, double-blind, placebo-controlled cross-over pilot study of glibenclamide in patients with septic shock

2005: Nathan Lawrentschuk - In-vivo tumour hypoxia, angiogenesis and characterisation of carbonic anhydrase IX expression with xenografted human Renal Cell Carcinoma in animal models using 124I-cG250 Positron Emission Tomography, Biodistribution, and Oxygen studies.

2006: Cris Cuthbertson - Capillary morphology is changed by severe acute pancreatitis and is improved by hyperbaric oxygen.

2007: Peter Wong (Basic Science Prize) - 18f-Fluorothymidine Positron Emission Tomography (Flt-Pet) As A Marker Of Cellular Proliferation In Renal Cell Carcinoma

Laurence Weinberg (Clinical Prize) - Pharmacoeconomics Of Inhalational Anaesthetics Agents: An 11-Year Cost Identification Analyses

2008: Russell Hodgson (Basic Science Prize) - Blockade with soluble ICOS-Ig prolongs survival of cellular xenografts

Julian Liew (Clinical Prize) - An anatomic feasibibility study: Nerve transfer to the triceps muscle using the posterior division of the axillary nerve.

2009: Russell Hodgson (Basic Science Prize) - Local Expression of ICOS-Ig Promotes Xenograft Survival Through The Induction of Regulatory T Cells

Simon Chong (Clinical Prize) - Minimally invasive measurement of cardiac output during surgery and critical care: A meta-analysis of accuracy and precision.
AUSTIN RESEARCH PRIZE - PAST WINNERS

2010: Russell Hodgson (Basic Science Prize) - ICOS-Ig Secreting Xenografts Have Prolonged Survival And Are Associated with Increased T Regulatory Cells And IL-10 Expression.

Vacchara Niumsawatt (Clinical Prize) - Risk factors of development of Acute Gangrenous Cholecystitis and its treatment outcomes

2011: Stanley Tay - SAVE Study: Reduced volatile agent usage following introduction of Et-control system

2012: Kapil Sethi - Comparison of Renal Preconditioning techniques in a rat model.

2013: Matthew Lee - Radial to femoral arterial blood pressure differences during liver transplantation surgery.

2014: Lawrence Lau - Assessment of Liver Remnant using ICG Clearance Intraoperatively during Vascular Exclusion: Early experience with the ALIVE technique.

Science never solves a problem without creating ten more.  
- George Bernard Shaw
Impact of blood flow occlusion on direct and indirect laser induced thermal liver injury

M Nikfarjam, C Malcontenti-Wilson, C Christophi.

BACKGROUND:
Laser, radiofrequency and microwave are common techniques for local destruction of liver tumours by focal hyperthermia. The main limitation of focal hyperthermia treatment is the volume of necrosis that can be achieved. Blood flow occlusion is commonly advocated as an adjunct to focal hyperthermia to increase the volume of tissue necrosis based on macroscopic and histological assessment of immediate or direct thermal injury. This study examines the impact of blood flow occlusion on direct and indirect laser induced thermal liver injury in a murine model using histochemical methods to assess tissue vitality.

METHODS:
Focal hyperthermia produced by laser (Nd-YAG - wavelength 1064 nm) was applied to the liver of inbred male CBA strain mice at 2W for 50 seconds (100J). Treatment was performed with and without temporary portal vein and hepatic artery blood flow occlusion. Animals were killed upon completion of the procedure to assess direct thermal injury and at 24, 48 and 72 hours to assess the progression of tissue damage. The maximum diameter of necrosis was assessed by vital staining for nicotinamide adenine dinucleotide (NADH) diaphorase. Microvascular changes were assessed by laser Doppler flowmetry, Confocal in-vivo microscopy and scanning electron microscopy.

RESULTS:
The direct thermal injury (mean(S.E.) assessed by NADH diaphorase staining was significantly greater following focal hyperthermia treatment without blood flow occlusion than with blood flow occlusion (3.3(0.4)mm vs. 2.9(0.3)mm; P=0.005). Tissue disruption, cracking and vacuolization was more pronounced adjacent to the fibre insertion site in the group treated with focal hyperthermia combined with blood flow occlusion. There was an equivalent increase in the extent of injury following therapy in both groups that reached a peak at 48 hours. The maximum diameter of necrosis in the focal hyperthermia alone group at 48 hours was significantly greater than the focal hyperthermia combined with blood flow occlusion group (5.8(0.4)mm vs.5.3(0.3)mm; P=0.011). The patterns of microvascular injury were similar in both groups, varying in extent.

CONCLUSIONS:
Temporary blood flow inflow occlusion appears to decrease the extent of initial injury measured by vital staining techniques and does not alter the time sequence of progressive tissue injury following focal hyperthermia therapy.

N Lawrentschuk, C Murone, AMT Poon, J Sachinidis, G O’Keefe, LG Johns-Putra, Z. LIU, I Davis, AM Scott, DM Bolton

BACKGROUND:
The purpose of our research is to evaluate oxygen levels and angiogenesis within renal cell cancers (RCC), as evidence suggests they are hypoxic, given their resistance to radiotherapy and chemotherapy. Hypoxia has now been shown in other tumours to correlate with resistance to treatment and poor prognosis. Our study builds on the finding of hypoxia in RCC and explores its relationship with immunohistochemical markers of hypoxia and a new novel marker of hypoxia in tumours, serum osteopontin

METHODS:
Patients who were undergoing radical nephrectomy for RCC had: 1) Evaluation of oxygen levels (pO2) within their renal cell cancers in vivo using a Polarographic Oxygen Sensor. 2) Immunohistochemistry including microvessel density to confirm at a sub-cellular level the relationship of hypoxia with the expression of proteins associated with hypoxia and angiogenesis in RCC and 3) Human osteopontin ELISA immunoassay techniques to analyse the serum levels of osteopontin.

RESULTS:
30 patients have been recruited thus far and we have demonstrated that RCC are relatively hypoxic (median pO2 7.2mmHg) compared to normal renal tissue (26.3mmHg). Microvessel density is increased in RCC compared to normal tissue indicating increased angiogenesis. Other markers if hypoxia were also increased. Serum osteopontin in patients with RCC was greater at 17.65 ± 5.3 ng/ml (mean ± 95% C.I.; range 5-41) compared to controls 8.75 ± 2.17 ng/ml (range 8-12).

CONCLUSIONS:
Renal cell cancers are relatively hypoxic and more angiogenic compared to normal tissue within the same kidney. This may explain resistance to radiotherapy and chemotherapy whilst helping to identify future therapeutic targets in the management of advanced renal cell cancer. Serum osteopontin has been demonstrated to be raised in RCC and is a novel tumour marker for renal cell carcinoma.
A randomised, double-blind, placebo-controlled cross-over pilot study of glibenclamide in patients with septic shock

Stephen Warrillow, Moritoki Egi, Rinaldo Bellomo

BACKGROUND:
Severe sepsis often causes a hypotensive shock state. Hyperpolarisation of the vascular smooth muscle cell membrane, due to the marked K+ efflux prevents Ca2+ entry into cells and may be responsible for ‘vasoplegia’. Glibenclamide (normally an oral hypoglycaemic agent) blocks the ATP-dependent K+ channel and may prevent hyperpolarization this restoring intra-cellular Ca2+ levels and re-sensitising vascular smooth muscle to noradrenaline. Animal studies have demonstrated that glibenclamide restores vascular sensitivity to noradrenaline. However, this effect has not been previously studied in humans.

Objective: To test whether glibenclamide restores noradrenaline responsiveness in septic shock patients.

METHODS:
Prospective, double-blind, placebo-controlled cross-over pilot study, in 10 patients with septic shock requiring an infusion of noradrenaline to receive either enteral glibenclamide 20mg or placebo. After twenty-four hours, each patient crossed over to receive the alternative therapy. The primary end-point was the change in noradrenaline infusion rate over time with maintenance of target mean arterial pressure. Secondary end-points included changes in heart rate and serum lactate levels.

RESULTS:
Glibenclamide was adequately absorbed enterally and, as expected, induced a significant decrease in serum glucose concentration (Mean glucose: 5.97 ± 2.17 vs 7.65 ±2.43 (P<0.0001) and increased the need for parenteral glucose administration. During glibenclamide treatment mean noradrenaline requirements fell from 13 to 4 µmol/min compared to a change from 19 to 7 µmol/L for placebo. The two changes represented a decrease of 78.9% and 71.1% in dose respectively (NS). There were also no significant changes in heart rate, mean arterial blood pressure and lactate concentration.

CONCLUSIONS:
Glibenclamide was well absorbed enterally and exerted its hypoglycaemic effect reliably. However, it failed to achieve a greater reduction in noradrenaline dose than placebo. Our observations suggest that, in septic humans, blockade of ATP-potassium dependent channels does not have a potent effect on vasomotor tone.
In-vivo tumour hypoxia, angiogenesis and characterisation of carbonic anhydrase IX expression with xenografted human Renal Cell Carcinoma in animal models using 124I-cG250 Positron Emission Tomography, Biodistribution, and Oxygen studies.

Nathan Lawrentschuk, C Murone, A Rigopolous, A Mountain, D Wang, G O’Keefe, G Jones, FT Lee, Ian Davis, Andrew M Scott, Damien M Bolton

BACKGROUND:
Hypoxia stimulates angiogenesis and has been demonstrated in tumours where it correlates with resistance to treatment and poor prognosis. We have demonstrated hypoxia in human Renal Cell Carcinoma (RCC). The purpose of animal models was to further evaluate oxygen levels within RCC whilst also focusing on expression of the protein carbonic anhydrase IX (CA IX). This protein is stimulated by hypoxia and involved in angiogenesis and may be a potential tumour target for imaging and future therapies. The human antibody cG250 binds to CAIX in vivo allowing biodistribution and PET studies when radiolabeled with iodine-124 (I124).

METHODS:
Balb/c nude mice had human RCC (SK-RC-52) xenografted subcutaneously. Tumours were grown to different volumes with oxygen levels measured. Further groups then had the radiolabelled monoclonal antibody 124I-cG250 (that binds to CA IX) injected intravenously and had Positron Emission Tomography (PET), gamma counting and oxygen studies performed on days 0, 1, 2, 3, 5, 7, 10 and 14 post injection. Immunohistochemistry and autoradiography was also performed.

RESULTS:
An inverse relationship between tumour volume and hypoxia within the model was established (P<0.001). Furthermore, CA IX was expressed by tumours with maximal uptake of 124I-cG250 on days 2/3 by distribution with gamma counting that could be correlated with uptake on PET imaging. Also, 124I-cG250 as read by gamma counter correlated with noninvasive PET scanning standardised uptake values of the radioisotope within tumours.

CONCLUSIONS:
The xenograft model confirms our previous findings that human RCC are relatively hypoxic compared to normal tissue. Also, that the level of hypoxia is inversely proportional to tumour size. CAIX was confirmed as an imaging and potential therapeutic target in RCC. Finally, a correlation was made between PET scanning with 124I-cG250 and biodistribution within tumours by gamma counting confirming the potential to serially PET scan animals rather than sacrifice in future biodistribution studies. This has major implications for animal ethics and the design of future biodistribution studies that are routinely used to characterised new radioisotopes and radiolabeled antibodies used to treat a variety of cancers.
Capillary morphology is changed by severe acute pancreatitis and is improved by hyperbaric oxygen.

C. Cuthbertson, K. Su, C. Malcontenti-Wilson, V. Muralidharan, C. Christophi

BACKGROUND:
Severe acute pancreatitis is characterized by alterations to the microcirculation, particularly affecting the capillary tree, which lead to pancreatic necrosis. The morphology of the pancreatic microvasculature is known to be affected in severe pancreatitis, but the effect of hyperbaric oxygen is unknown. The aims of this study are to determine the progression of pancreatic microvascular changes caused by acute pancreatitis and to determine the effect of the administration of hyperbaric oxygen (HBO).

METHODS:
Sixty seven male Wistar rats weighing 250-350g were induced with severe pancreatitis by bilio-pancreatic infusion of 4% sodium taurocholate. Animals were randomised to either HBO treatment or control. HBO treatment (100% oxygen for 90 minutes at 2.5 Atmospheres) was commenced 6 hours following induction of pancreatitis, and continued 12-hourly. Surviving animals underwent microvascular polymer casting of the pancreas at six, 24, 48 and 72 hours following commencement of treatment, and equivalent time points for control animals. Normal and Sham-operated animals also underwent casting. Microvascular casts were created by the injection of freshly prepared Mercox resin through a cannula in the thoracic aorta. The pancreas was removed after 24 hours of polymerisation and further prepared for scanning electron microscopy of the resin cast. Scanning electron micrographs of the casts were compared for capillary density, poor capillary filling, vessel diameter, and major morphological changes.

RESULTS:
Normal pancreatic microvascular casts showed a dense network of capillaries, with multiple anastomoses (Image 1). Significant morphological changes appeared at 24 hours post induction (Image 2). Microvascular casts demonstrated poor capillary filling, decreased capillary density and increased capillary cast diameter. Capillary diameter was increased (from 6.7µm to 10.3µm at 24hr, p<0.01, and 11.8µm at 48hr, p<0.001), capillary heterogeneity was increased (range increased from 13.8µm to 21.4 µm, p<0.001) and capillary density was reduced (from 1140µm-² to 758µm-², p<0.01). These changes occurred at 24 hours post induction and were maintained at 48 and 72 hours. Treatment with HBO reduced the severity of microvascular morphological changes at each time point (Image 3). These changes became apparent at 48 hours post induction, and were maintained at 72 hours. At 48 hours, capillary diameter was decreased toward normal (from 11.8µm to 8.4µm, p<0.01), range was reduced, and capillary density was increased (from 722µm-² to 901µm-², p<0.01).

CONCLUSIONS:
Microvascular parameters are affected by acute pancreatitis, with changes detected at 24 hours and maintained until at least 72 hours. HBO improves the microvascular morphology parameters in acute pancreatitis towards normal values. HBO has potential as a unique alternative therapy in acute pancreatitis.
18f-Fluorothymidine Positron Emission Tomography (Flt-Pet) As A Marker Of Cellular Proliferation In Renal Cell Carcinoma

Wong P1,2; Lee ST2,3,4; Eng J3; Berlangieri SU2; Pathmaraj K3; O’Keefe GJ3; Byrne AJ3; Lawrentschuk N1,2; Davis ID2; Bolton DM1; Scott AM2,3,4.

1 Department of Surgery (Urology), University of Melbourne, Austin Health, Heidelberg, Australia. 2 Ludwig Institute for Cancer Research, Austin Health, Heidelberg, Australia. 3 Centre for PET, Austin Health, Heidelberg, Australia. 4 Department of Medicine, University of Melbourne, Austin Health, Heidelberg, Australia.

BACKGROUND:
18F-FLT-PET (Fluorothymidine Positron Emission Tomography) has been used to non invasively measure cellular proliferation in a number of tumour types. However, its role in renal cell carcinoma (RCC) has not been established. We aim to assess FLT-PET in RCC, and to compare it to immunohistological measurements of proliferation.

METHODS:
Patients with suspected RCC suitable for nephrectomy had preoperative FLT and FDG (fluorodeoxyglucose) PET/CT scans. Surgical samples were obtained for immunohistochemical analysis (Ki-67). Qualitative visual grading relative to normal kidney and analysis of maximum standardized uptake value (SUVmax) of each PET scan was assessed using co-registered low-dose 5mm CT and prior triple phase CT imaging. Uptake in RCC using FLT PET was compared to FDG PET. Statistical analysis comparing Ki-67 and SUVmax was performed.

RESULTS:
A total of 19 patients (13 clear cell, 5 papillary and 1 transitional cell carcinoma) underwent preoperative PET scans, with immunohistochemical data available for 13. Visual grading found most tumours had radiotracer uptake that was equal or less than the contralateral kidney. FLT uptake was generally less than FDG. Bivariate analysis showed a positive correlation between Ki-67 & FLT SUVmax (p-value 0.001, r = 0.8) and between Ki-67 & FDG SUVmax (p-value 0.005, r = 0.73).

CONCLUSIONS:
Uptake of FLT in RCC is less than FDG. There is positive correlation between FLT uptake and Ki-67 proliferative index in RCC suggesting that the degree of proliferation within RCC can be predicted by PET imaging. Further study is required to determine whether this correlates with patient outcome.
Pharmacoeconomics Of Inhalational Anaesthetics Agents: An 11-Year Cost Identification Analyses

Laurence Weinberg, David Story, Larry McNicol

BACKGROUND:
Anaesthetic departments account for 2-3% of the total hospital budget, with anaesthetic drugs accounting for 5-8% of total pharmacy expenditure. Inhalational agents account for 20% of anaesthetic drugs therefore are one of the areas that are most amenable to immediate cost reduction in the anaesthetic department budget. This study is a cost identification analyses assessing inhalational anaesthetic agent expenditure at Austin Health over an 11-year period. Pharmacoeconomic modeling is used to evaluate strategies to curtail costs.

METHODS:
The number of bottles utilised of three volatile agents (Isoflurane, Sevoflurane, Desflurane) was collected each month for the financial years ending 1997 to 2007. The acquisition costs and the cumulative drug expenditure in dollars for each agent were calculated. Inhalational agent utilisation patterns and unit price changes were evaluated. Pharmacoeconomic modeling using low fresh gas flow anaesthesia was performed to evaluate practical methods for reducing anaesthesia costs. The rational use of the cheaper generic volatile agent Isoflurane was used in pharmacoeconomic cost-containment strategy models.

RESULTS:
For the financial years ending 1997 to 2007, pharmacy acquisition costs for a bottle of Isoflurane (250mL), Sevoflurane (250mL) and Desflurane (240mL) were $157, $336, $170 respectively, and for the financial years ending 2005 to 2007, cost per bottle was $109, $265, $180 respectively. The number of bottles of Isoflurane decreased from 384 bottles/year in 1997 to 204 bottles/year in 2007. The number of bottles of Sevoflurane increased from 226 bottles/year in 1998 to 875 bottles/year in 2007. Desflurane use commenced at Austin Health in 2002 with 34 bottles being used. This increased to 163 bottles/year in 2007. Expenditure for Isoflurane decreased from $88,985/year in 1997 to $22,006/year in 2007. In contrast, Sevoflurane expenditure increased from $11,442/year in 1997 to $274,692/year in 2007. Desflurane expenditure increased from $5,855/year in 2002 to $29,340/year in 2007. Total cumulative expenditure for inhalational agents was $100,427/year in 1997, increasing to $326,038/year in 2007. Pharmacoeconomic modelling demonstrates that the cost of an inhalational agent for a 60-minute anaesthetic, at 1 Minimum Alveolar Concentration, at fresh gas flows of 1L/min (low flow), is $1.54 for isoflurane and $6.89 for Sevoflurane. At fresh gas flows of 6 L/min (high flow), costs increase to $9.20 for Isoflurane and $47.47 for Sevoflurane. Cost modelling reveals if Sevoflurane usage between 1997 and 2007 would have been reduced by 40% per year and substituted for the cheaper inhalational agent Isoflurane, a total savings of $866,565 would have been achieved for this 11-year period. Similarly, conservative cost analyses predicts that if the current trends in volatile anaesthetic agents continue at Austin Health over the next 10 years, if a 40% reduction per year in Sevoflurane usage could be achieved by utilising Isoflurane in its place, a total net savings in excess of $1.8 million will result.

CONCLUSIONS:
Cost analyses of anaesthetic drugs is necessary is today’s economic climate. Low flow anaesthesia is a simple but highly effective method of cost minimization for inhalational anaesthetic agents. Cost containment is also influenced by the rational use of available inhalational agents.
An anatomic feasibility study: Nerve transfer to the triceps muscle using the posterior division of the axillary nerve.

Liew J H, van Zyl N

BACKGROUND:
This study proposes the co-aptation of the posterior division of the axillary nerve to the lateral head of triceps nerve as a new, alternative option for triceps reconstruction in the tetraplegic patient. This study provides anatomical data in order to appraise the feasibility of nerve transfer to the triceps using the posterior division of the axillary nerve.

METHODS:
Morphologic features of the axillary nerve from the quadrangular space and the radial nerve from the triangular space were studied in 9 cadaveric arms under 2.0x loupe magnification. Nerve lengths, diameters, and branches were recorded.

RESULTS:
Average arm length was 312 mm. The average diameter of the posterior division of the axillary nerve was 2.5 mm whilst that of the lateral head of triceps nerve was 2.1 mm. Nerve transfer was possible in all upper limbs except one where no branch to the lateral head of triceps could be identified. In full adduction the average overlap of the nerve transfer was 16.75mm, whereas, when the arm was abducted to 90 degrees, the average amount of nerve overlap was 10.5mm.

CONCLUSIONS:
Nerve transfer from the posterior division of the axillary nerve to the lateral head of triceps is anatomically possible. It provides a possible alternative to reconstruct elbow extension with the advantages of preserving the anatomy and biomechanics of the native muscles, avoiding the need for synthetic prosthesis as well as avoiding donor defects from tendon graft harvest.
Blockade with soluble ICOS-Ig prolongs survival of cellular xenografts

Hodgson R, Christiansen D, Ierino FL, Sandrin MS

BACKGROUND:
Xenografts are one possible solution to the lack of donor organs for diseases such as Diabetes Mellitus. T cell costimulatory pathways are integral to acute cellular rejection against these grafts. Inducible Co-Stimulator (ICOS) pathway blockade has been shown to prolong allograft survival, but there is limited data for xenograft models. Our hypothesis is that local expression of the fusion molecule ICOS-Ig by cells in allograft or xenograft models will prolong survival of cellular grafts.

METHODS:
Porcine Iliac Endothelial cells (PIEC) were transfected with cDNA of the fusion molecule ICOS-Ig. Intracellular and secreted expression was confirmed and quantified using immunoperoxidase staining and Western Blot analysis. In vitro testing of supernatant in mixed lymphocyte reactions was performed. In vivo survival was examined using a subcutaneous graft model in mice.

RESULTS:
ICOS-Ig containing supernatant gave a 99.5% reduction in proliferation of an allograft mixed lymphocyte reaction. Similarly, xenogeneic proliferation was inhibited by 84.3%. In addition an 84.5% reduction in proliferation was observed when PIEC expressing ICOS-Ig were used as stimulators. PIEC-ICOS-Ig xenografts showed prolonged survival compared to wild-type PIEC xenografts (mean survival 34 vs 12 days, p=0.0025) in a subcutaneous graft models in Balb/c mice.

CONCLUSIONS:
Blockade of T cell co-stimulation by the fusion molecule ICOS-Ig has been demonstrated to decrease proliferation in allograft and xenograft in vitro models. Further, there is significant prolongation of survival of PIEC transfected with ICOS-Ig in vivo. These data suggest that further investigations for the role of T cell co-stimulatory blockade in xenografts, through the local expression of ICOS-Ig, are warranted.
Minimally invasive measurement of cardiac output during surgery and critical care: A meta-analysis of accuracy and precision.

Philip J Peyton, Simon Chong.

BACKGROUND:
When assessing the accuracy and precision of a new technique for cardiac output measurement, the commonly accepted criterion for acceptability of agreement with a reference standard is that the percentage error (95% limits of agreement/mean cardiac output) should be 30% or less. We reviewed published data on four different minimally invasive methods adapted for use during surgery and critical care: pulse contour techniques, esophageal Doppler, partial carbon dioxide rebreathing, and transthoracic bio-impedance, to assess their bias and percentage error in agreement with thermodilution.

METHODS:
An English language literature search identified published papers since 2000 which examined the agreement in adult patients between bolus thermodilution and each method. For each method a parametric assessment was performed using studies in which the first measurement point for each patient could be identified, to obtain a pooled mean bias and percentage error weighted according to the number of measurements in each study.

RESULTS:
47 studies were identified as suitable for inclusion: N studies, n measurements: mean weighted bias [% error] were: pulse contour N = 25, n = 714: 0.1 L/min [40.7%]; esophageal Doppler N = 2, n = 57: -0.8 L/min [42.1%]; partial CO2 rebreathing n = 145: 0.0 L/min [43.6%]; transthoracic bio-impedance N = 13, n = 435: -0.1 L/min [42.9%];

CONCLUSIONS:
No method has achieved agreement with bolus thermodilution which meets the expected 30% limits. The relevance in clinical practice of these arbitrary limits should be reassessed.
Local Expression of ICOS-Ig Promotes Xenograft Survival Through The Induction of Regulatory T Cells

Hodgson R, Ziolkowski A, Christiansen D, Simeonovic C, Ierino F, Sandrin M

BACKGROUND:
Xenografts are one possible solution to the lack of donor organs for diseases such as Diabetes Mellitus. The acute cellular rejection of xenografts is one of the critical processes that must be overcome. We have previously shown that blockade of T cell co-stimulation with locally expressed ICOS-Ig can prolong the survival of cellular xenografts. The mechanisms for this prolongation of survival have hitherto remained unknown, with the induction of regulatory T cells (Tregs) being one possibility. Tregs, through their secretion of IL10, TGFβ and interferon-γ, suppress activated T cells to downregulate the immune response, and may also have a role in tolerance to transplanted grafts. We show here that locally expressed ICOS-Ig induces Tregs and prolongs cellular xenograft survival.

METHODS:
Porcine Iliac Endothelial cells (PIEC) were transfected with cDNA encoding the fusion molecule ICOS-Ig. Subcutaneous xenograft transplants with wild-type PIEC or PIEC-ICOS-Ig were performed in BALB/c mice; either single grafts, or a dual graft model with a wild-type PIEC graft on one flank and a PIEC-ICOS-Ig on the opposing flank. Grafts were sampled for immunohistochemistry and real-time PCR at days 7 and 14, with overall survival also being measured.

RESULTS:
Locally expressed ICOS-Ig prolongs xenograft survival when compared with wild-type grafts (median survival 34 vs 12 days, p=0.0025). When wild-type PIEC and PIEC-ICOS-Ig cells are grafted in the same mouse, wild-type PIEC graft survival is prolonged (median survival 28 vs 12 days, p<0.05), indicating a systemic effect of ICOS-Ig. Increased numbers of Tregs were found in the perigraft region of wild-type PIEC grafts in the dual graft model when compared with wild-type PIEC single grafts at days 7 and 14.

CONCLUSIONS:
Locally expressed ICOS-Ig prolongs survival of cellular xenografts, with the mechanism both local and systemic. The presence of ICOS-Ig induces perigraft Tregs which are associated with prolonged survival of xenografts. These data suggest that locally expressed ICOS-Ig may play an important role in prolonging xenograft survival and the induction of tolerance through the presence of Tregs.
Risk factors of development of Acute Gangrenous Cholecystitis and its treatment outcomes

V Niumsawatt.

BACKGROUND:
Gangrenous cholecystitis is considered a more severe form of acute cholecystitis. The risk factors associated with this condition and its impact on morbidity and mortality compared to non-gangrenous acute cholecystitis is poorly defined.

METHODS:
Patients with histologically confirmed acute cholecystitis treated between 2005-2010 were identified from a prospectively maintained database. Those with gangrenous cholecystitis were then compared to those with non-gangrenous acute cholecystitis.

RESULTS:
184 patients with non-gangrenous acute cholecystitis and 106 patients with gangrenous cholecystitis were identified. The risk factors associated with gangrenous cholecystitis included older age (P 0.001), diabetes (P 0.049), delay in operation (P <0.001), temperature of >38°C (P <0.001), tachycardia (P 0.002), detection of muscle rigidity on examination (P 0.01), elevations in white cell count (WCC) (P <0.001), C-reactive protein (CRP) (P 0.001), bilirubin (P 0.029) a GGT (P <0.001), and elevated urea and creatinine. (P <0.05). There was no overall difference in complications between the two groups. There was a lower incidence of common bile duct stones in the gangrenous cholecystitis group (25% versus 13% P = 0.017). Gangrenous cholecystitis was however associated with an increase in post-operative ICU/HDU requirement (P 0.023) and was associated with increased mortality (P 0.017).

CONCLUSIONS:
Gangrenous cholecystitis has certain clinical features and associated laboratory findings that may help differentiating it from non-gangrenous cholecystitis. It is associated with a higher incidence of mortality. Minimizing a delay in operative management, which is noted in this condition may potentially improve treatment outcomes.
ICOS-Ig Secreting Xenografts Have Prolonged Survival And Are Associated with Increased T Regulatory Cells And IL-10 Expression

Hodgson R, Christiansen D, Ziolkowski A, Mouhtouris E, Simeonovic C, Ierino F, Sandrin M

BACKGROUND:
Many patients die waiting for organ transplantation due to a lack of donor organs. Xenografts are an unlimited resource, however solutions to barriers such as acute cellular rejection have yet to be elucidated. T regulatory cells (Tregs), through their secretion of IL10, TGFß and interferon-Î¼, suppress activated T cells to downregulate the immune response seen in acute cellular rejection, and may also have a role in tolerance to transplanted grafts. We have previously shown that blockade of T cell co-stimulation with locally expressed ICOS-Ig can prolong the survival of cellular xenografts and now show that this response is xeno-specific and associated with increased IL-10 expression and induction of Tregs.

METHODS:
Porcine Iliac Endothelial cells (PIEC) were transfected with cDNA encoding the fusion molecule ICOS-Ig. Subcutaneous xenograft transplants with wild-type PIEC or PIEC-ICOS-Ig were performed in BALB/c mice; either single grafts, or a dual graft model with a wild-type PIEC graft on one flank and a PIEC-ICOS-Ig on the opposing flank. Grafts were sampled at days 7 and 14 and characterised with immunohistochemistry, flow cytometry and Q-PCR.

RESULTS:
Locally expressed ICOS-Ig prolonged xenograft survival when compared with wild-type grafts (median survival 34 vs 12 days, p=0.0025). When wild-type PIEC and PIEC-ICOS-Ig cells were grafted in the same mouse, wild-type PIEC graft survival is prolonged (median survival 28 vs 12 days, p<0.05), indicating a systemic effect of ICOS-Ig. This result was found to be xeno-specific, with no prolongation of similarly grafted EL4 allografts. Immunohistochemistry revealed increased numbers of FoxP3+ cells in the perigraft region of both PIEC-ICOS-Ig grafts and dual PIEC and PIEC-ICOS-Ig grafts at days 7 and 14. Flow cytometry of the graft infiltrating lymphocytes revealed the majority of these FoxP3+ cells to be of the CD4+CD25+FoxP3+ Treg phenotype. Furthermore, Q-PCR of these grafts revealed differences in expression of IL-10 but not TGFß or IFN-Î¼.

CONCLUSIONS:
The presence of ICOS-Ig induces perigraft Tregs which are associated with prolonged survival of xenografts. The increased expression of IL-10 in these grafts indicates a critical role of T cell/macrophage binding and antigen recognition in the presence of ICOS-Ig. These data suggest that locally expressed ICOS-Ig may play an important role in prolonging xenograft survival and the induction of tolerance through the presence of Tregs.
SAVE Study: Reduced volatile agent usage following introduction of Et-control system

Stanly Tay¹, Laurence Weinberg², Phil Peyton²; Juris Briedis³

¹Anaesthetic Registrar, Austin/Northern Health ²Staff Anaesthetist, Department of Anaesthesia, Austin Health ³Director of Anaesthesia & Perioperative Medicine, Northern Health

BACKGROUND: Total cumulative expenditure for inhalational agents at Austin Hospital was $270,000 for the 2010 financial year. Anaesthesia pharmacoeconomic modelling in our department shows that inhalational agent costs will continue to escalate whilst resources remain finite. In order to evaluate strategies to reduce costs within a finite hospital budget, we hypothesised that the use of Et control on the Aisys Carestation anaesthesia delivery system (GE Healthcare®) during volatile anaesthesia will significantly reduce usage compared to current practice. The Aisys Carestation is an anaesthesia delivery system designed to minimise fresh gas and volatile usage by achieving and maintaining set target values using an automated algorithm with low-flow anaesthesia.

METHODS: Following ethics approval, numbers and duration of volatile general anaesthesia cases, along with volatile costs and CO2 absorbent costs were reviewed from Health Information Service and Pharmacy in a 12-week period prior to and a 12-week period after the introduction of Et-control. Inclusion criteria were all general anaesthesia requiring a volatile agent. Primary end-point was average cost per day of volatiles. We also surveyed Et-control use, looking at rates of utilisation plus flow rates used, to determine the generalisability of our findings.

RESULTS: Over the two time periods, there were 1818 vs. 1810 cases analysed with no statistical difference between gender (p=0.32), age group (p=0.87), ASA scores (p=0.73) or mean workload (153 vs. 160 hr/wk, p=0.37). Use of Et control on the Aisys Carestation anaesthesia delivery system showed a substantial reduction in inhalational agent cost ($376/day vs. $316/day, p=0.01) representing a 19.7% daily cost reduction when corrected for number of anaesthesia hours. Sevoflurane use was 182 bottles (45.5L) vs 148 (37L), Desflurane the same at 20 (4.8L), and Isoflurane the same at 1 (0.25L). CO2 absorbent cost did not increase significantly ($0.07/day). Our survey had a 65% response rate (1169/1810), and showed Et-control was used in 89% of cases, with a mean flow rate of 0.63 vs 3.2L/min.

CONCLUSIONS: Low flow anaesthesia is a simple but highly effective method of cost minimisation for inhalational anaesthetic agents. Use of Et-control on the Aisys Carestation anaesthesia delivery system significantly reduces volatile cost compared to previous routine practice. Real cost savings were approximately 20% or $35,000 per 10,000 general anaesthetic hours.
Comparison of Renal Preconditioning techniques in a rat model.

K Sethi, O Patel, J Ischia, L Xiao, G Baldwin, A Shulkes, DM Bolton

BACKGROUND: Renal preconditioning (RPC) is a technique that exposes tissue susceptible to ischaemia into triggering a family of intracellular transcription factors, the Hypoxia Inducible Factors (HIFs), to protect against kidney injury. Preconditioning may offer protection to cells against irreversible nephron loss and tolerate ischaemia beyond the accepted critical ischaemia time. Whilst these techniques have been explored in other organs, no study has compared the effects of these techniques in the kidney. There is also emerging evidence that a combination of these preconditioning techniques may confer greater protection in tissue.

METHODS: 24 solitary kidney-model Sprague Dawley rats were divided into groups of 6 undergoing either a) control, b) 30mg/kg subcutaneous cobalt chloride (CoCl$_2$) treatment over 24 hours, c) intermittent clamping (IC) consisting of 5 minutes renal artery clamping followed by 10 minutes reperfusion over 4 cycles, or d) a combination of both CoCl$_2$ and IC. Following preconditioning, all rats underwent 40 minutes of renal artery clamping (critical ischaemia) and were followed up with serum renal function tests and animal health scores for 7 days.

RESULTS: All rats demonstrated the greatest rise in serum creatinine at 24 hours, and urea at 72 hours with a return to basal levels by day 7. All preconditioning methods improved renal function following critical ischaemia up to 72 hours (mean +/- SEM creatinine in mmol/l: control group, 273.3 +/- 40.3; CoCl$_2$, 76.3 +/- 10.7 p<0.0005; IC, 76.3 +/- 36.2 p<0.05; combination, 271.1 +/- 76). Rats treated with CoCl2 had the lowest rise in serum creatinine at 24 hours (Control 390.5 +/- 18.4; CoCl$_2$, 144.7 +/- 31.5 p<0.0001). Whilst the control group had a 50% mortality rate, no rats in the preconditioning groups died (p<0.005).

CONCLUSIONS: Individual cobalt treatment offers greater protection against renal damage than intermittent clamping or a combination of these techniques in the kidney. Development of similar agents that specifically target the same mechanistic pathway of HIF activation would offer the greatest benefit in renal preconditioning for clinical application. An approach that stimulates kidney cells into protecting themselves by preconditioning prior to ischaemic damage has great promise for use in a wide variety of medical and surgical conditions in the future.
Radial to femoral arterial blood pressure differences during liver transplantation surgery.

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BACKGROUND: Maintenance of cardiovascular stability during orthotopic liver transplantation (OLTx) is a significant challenge to the anaesthetist. Accurate real-time monitoring of the circulation is essential for the optimisation of blood volume status and titration of vasopressor support to minimise circulatory instability and reduce perioperative risk. Discrepancies in arterial blood pressure measurements at different measurement sites have been demonstrated in vasodilated states during cardiac surgery. A small number of published studies in OLTx have shown mixed results. This has important implications for anaesthetic practice, as measured arterial blood pressure is a primary determinant of fluid and vasopressor administration. We compared arterial blood pressure measurements in the radial and femoral arteries during OLTx to determine whether significant discrepancies between them exist, and whether arterial blood pressure measurements at the two sites can be used interchangeably.

METHODS: Twenty-five patients were enrolled. Radial and femoral arteries were cannulated with a standardised arterial line kit. Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP) and pulse pressure (PP) were measured at four time points. For each patient, an overall difference in each blood pressure parameter was calculated by averaging across the four time points. Agreement between arterial sites was assessed by the method described by Bland and Altman. Correlation was assessed by Pearson’s correlation coefficient.

RESULTS: Overall radial to femoral arterial pressure differences are expressed as mean difference, standard deviation and percentage error.

SBP: -14.9mmHg, 24.8mmHg, 47.0%; DBP: -2.0mmHg, 5.2mmHg, 20.8%
MAP: -4.8mmHg, 4.5mmHg, 13.1%; PP: -13.5mmHg, 25.5mmHg, 91.8%

CONCLUSIONS: In patients undergoing liver transplantation, SAP and PP values from the radial artery neither agree nor correlate with femoral artery values. Insertion sites cannot be used interchangeably for these measurements. For MAP and DAP, radial and femoral sites can be used interchangeably. The observed difference in central and peripheral arterial pressures has implications for the accuracy of devices that derive haemodynamic parameters from pulse waveform analysis.
Assessment of Liver Remnant using ICG Clearance Intraoperatively during Vascular Exclusion: Early experience with the ALIIVE technique.

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BACKGROUND: The most significant risk following major hepatectomy is post-operative liver insufficiency. Current preoperative assessment of the future liver remnant (FLR) relies upon assumptions which may not be valid in the setting of advanced resection strategies. Post-operative indocyanine green (ICG) clearance has recently been shown to be the earliest and most accurate marker for liver insufficiency after hepatectomy. This report describes and assesses the feasibility of the ALIIVE technique, which replicates the post-hepatectomy state intraoperatively, prior to vascular division, for functional FLR evaluation with ICG clearance.

METHODS: Ten patients undergoing planned major liver resection (hemihepatectomy or greater) were recruited. Routine preoperative assessment included CT and standardized volumetry. ICG clearance was measured noninvasively using a finger spectrophotometer at various timepoints including following parenchymal transection during in-flow and out-flow occlusion before vascular division, the ALIIVE assessment. Outcome parameters were post-hepatectomy liver failure and post-operative mortality.

RESULTS: There was one mortality and three cases of post-hepatectomy liver failure. The patient who died had the lowest ALIIVE ICG clearance (7.1%/min vs 14.4 +/- 4.9). Routine preoperative CT and standardized volumetry did not predict outcome.

CONCLUSIONS: The novel ALIIVE technique is feasible and uniquely assesses actual future liver remnant function before the point of no return during major hepatectomy. This technique may be useful as a check-step to offer a margin of safety to prevent post-hepatectomy liver failure and death.
Surgery and Scientific Research: Why do it?  
Research Opportunities & The Academic Research Program

The Austin Hospital is a major hub for surgical training with 45 General Surgery training positions and many others within the surgical subspecialties. The commitment of the Department of Surgery towards surgical education and research provides excellent opportunities for the trainees at every level. We also endeavour to establish strong links with other departments to develop collaborative research including the Peter McCallum Hospital, Ludwig Institute for Cancer Research, and clinical departments such as Anaesthesia, Radiology, Oncology and Intensive Care.

Research Opportunities for Surgical Trainees: The department strongly encourages surgical trainees to undertake formal research in the form of full time research higher degrees. Alternatively they may undertake research concurrent with their clinical activities. Research activity has progressively increased in importance to the surgical trainee over the past years as more emphasis has been placed on a scientific approach to surgical problems. Increasing demands are made on trainees to conduct, present and publish on surgical research not only as a component of their accredited training but also to increase their career opportunities and successful applications for future fellowships. The Department of Surgery continues to strongly support research undertaken by trainees either as full time research higher degrees or on a smaller scale during their clinical tenure.

Trainees at all levels from junior hospital medical officers to advanced SET trainees are encouraged to seek opportunities early in the year to begin work on at least one research project. If trainees have a particular interest in a subspecialty, they are encouraged to approach members of that unit for a potential research project. If not, the Department of Surgery will be able to provide a number of options for small, relevant clinical studies based on our ongoing prospective data collection service. The aim would be to present the results at the Austin Research Prize presentation and subsequently to have it published in a relevant peer reviewed journal. The presence of ongoing active laboratory based research projects, a comprehensive general surgical database and the access to surgical tissue samples from the Victorian BioBank provide a wide variety of opportunities in clinical and basic science research. This allows research projects to be tailored to the trainees expectations and level of experience. Trainees who undertake research have the opportunity to present their results at Austin Research Week as well as the annual Austin Research Prize in Surgery and Anaesthesia.

Scholarship support for surgical trainees undertaking full time research is readily available from the generous support of the Royal Australasian College of Surgeons as well as The University of Melbourne Melville Hughes Scholarship.

Research Higher Degree (RHD) Program
The Department of Surgery strongly encourages higher degrees by research (PhD, MPhil, DMedSc and MSurg). The main focus of such research is related to cancers and diseases of the liver, pancreas and biliary tree, organ transplantation, renal and prostate cancer, and spinal cancer and biology. Students from both medical or biomedical fields are welcome. Basic laboratory science projects include techniques such as in vivo animal models, molecular biology, histopathology and microscopy, and in vitro cell culture. Clinical research includes PET imaging, retrospective studies and laboratory work with human samples from the Victorian Cancer Biobank.

Expectations and Outcomes of Research
The University of Melbourne is recognised internationally as a leader in graduate research. As one of our students, you will enjoy opportunities to work with leading researchers in first rate facilities, developing skills essential to your future career. The departmental philosophy supports the timely completion of all research undertaken by providing the necessary facilities, mentorship, technical expertise and funding support. Researchers are expected to present their results at local, national or international meetings and are strongly encouraged to publish their work in peer reviewed journals.
I will not say I failed a thousand times. I will say that I discovered there are thousand ways that can cause failure

- Thomas Edison

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