PENTOSAN POLYSULFATE PRIMED MESENCHYMAL PROGENITOR CELLS PROMOTE INTERVERTEBRAL DISC REPAIR FOLLOWING MICROSIDECTOMY IN AN OVINE MODEL

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Introduction: Lumbar microdiscectomy addresses neural compression but fails to halt disc degeneration. 10–20% of patients subsequently develop debilitating back pain and approximately 15% undergo further surgical intervention. Pre-incubation of mesenchymal precursor cells (MPCs) with pentosan polysulfate (PPS) enhances viability and chondrogenic differentiation, but inhibits osteogenesis. This study investigated the potential of PPS primed mesenchymal precursor cells (pMPCs) to facilitate disc repair in an ovine model.

Methods: Eighteen adult ewes randomly assigned into three groups underwent pre-operative MRI followed by lumbar microdiscectomy at two levels. The injured control (IC) group received no further treatment; the MPC group were implanted with non-primed MPC + scaffold; the pMPC group received the pMPC + scaffold. At six months MRI, gross morphological, histological and biochemical analysis was completed.

Results: MPC and pMPC discs demonstrated reduced degeneration as assessed by disc height loss (p < 0.05) and Pfirrmann grades (p < 0.001) relative to IC discs. On gross morphology pMPC disc segments were significantly less degenerate than IC discs (p = 0.019). Proteoglycan content of pMPC discs was significantly greater than IC discs and not significantly different to controls for the injured annulus fibrosus (AF) region and nucleus pulposus (NP) region contralateral to the injury. DNA content for pMPC discs was significantly less than IC discs for the NP & AF injury and adjacent regions. On histology pMPC discs demonstrated increased organization and decreased degeneration while MPC discs displayed increased vascular infiltration.

Conclusion: pMPCs post microdiscectomy reduced disc degeneration, improved disc height and matrix organisation, NP proteoglycan content and histological degeneration relative to microdiscectomy alone.

IN SITU BIOSCAFFOLD 3D PRINTING FOR CARTILAGE REGENERATION IN A LARGE ANIMAL MODEL

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Introduction: In-situ 3D printing is an exciting bio-fabrication technology to deliver tissue-engineering techniques by the surgeon at the time and location of need. We have created a hand-held extrusion ink-jet printing device (Biopen) that allows the simultaneous and co-axial extrusion of Bioscaffold and cultured cells directly into the defect that needs to be repaired. This pilot study aimed at assessing the use of the Biopen in vivo to repair a full thickness chondral defect in a large animal model.

Methods: An 8-mm circular critical sized full thickness chondral defect has been created in the weight-bearing surface of the lateral and medial condyles of both femurs of 8 sheep. Each defect has been treated with either (i) - hand-held in situ 3D printed bioscaffold using the Biopen (HH group), (ii) pre-constructed bench-based printed bioscaffolds (BB group), (iii) microfractures (Clinical Group) or (iv) left untreated (Negative Control Group). Histology and IHC have been performed in the retrieved condyles (O’Driscoll score) and biomechanical indentation tests have been performed to assess the physical properties of the regenerated cartilage tissue.

Results: The HH printed scaffolds (i) remained in place for the duration of the experiment (8 weeks), (ii) do not induce inflammatory reaction, (iii) allow early cartilage formation which shows superior macroscopic and microscopic score when compared to microfractures.

Conclusion: This pilot study shows that direct in-situ bioprinting can be used to regenerate articular cartilage with superior results when compared to the clinically available surgical techniques.

TAMOXIFEN EXERTS ANTI-PROLIFERATIVE EFFECTS IN OESOPHAGEAL ADENOCARCINOMA CELLS BY MODULATION OF ERA AND ERB ISOFOMS

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Introduction: Previously, we reported that the oestrogen receptor (ER) modulator tamoxifen is cytotoxic in oesophageal adenocarcinoma (OAC) cells. We also found that OAC cells express a number of ERα and ERβ isoforms, differing in molecular weight, which are common to isoforms found in breast cancer. In addition to its cytotoxicity (killing cancer cells), a major component of the activity of tamoxifen is via anti-proliferative effects (inhibiting cancer growth). These properties are effected by ERα and ERβ isoforms, which have proven functional roles in mediating tamoxifen response in breast cancer. For instance, 46 kDa ERβ mediates anti-proliferative responses to tamoxifen, and 36 kDa ERα confers resistance. Full-length 59 kDa ERβ is known to inhibit cancer growth. Here, we investigate the anti-proliferative effects of tamoxifen in OAC cells and identify associations between ER isoforms and response.

Methods: OAC and breast cancer cell cultures were treated with sub-cytotoxic concentrations of tamoxifen metabolites 4-hydroxytamoxifen (4-OHT) and endoxifen for 120 hours. Sub-lethal drug concentrations were chosen to inhibiting cell growth but not kill cells directly, so that effects upon ER isoform expression in living cells could be assessed. Proliferation and caspase 3/7 (a mediator of apoptosis) activation were assessed with an Incucyte FLR live cell imaging platform. ER expression in tamoxifen-treated or control cultures was profiled by Western blot analysis.

Results: The most sensitive cell lines (% survival fraction vs control at 120 hours for 4-OHT, endoxifen) were OAC cell lines OE-19 (40.4, 33.2) and Flo-1 (58.7, 34.2), and breast cancer cell line MCF-7 (44.6, 31.5). These cell lines also showed the greatest levels of caspase activation. The 90 and 46 kDa isoforms of ERα were associated with sensitivity to tamoxifen. The 36 kDa isoform of ERα was associated with resistance to tamoxifen. Drug response was accompanied by downregulation of the 90, 66, 50, and 36 kDa isoforms of ERα, and upregulation of 59 kDa ERβ, in both oesophageal and breast cancer cells.

Conclusion: The activity of tamoxifen in OAC cells involves anti-proliferative and cytotoxic effects which appear to be mediated by drug modulation of ERα and ERβ isoforms. This is in keeping with literature surrounding the functions of the 46 and 36 kDa ERα isoforms in tamoxifen response, the role of 59 kDa ERβ in inhibiting cancer growth, and the mechanism of endoxifen in downregulating ERα.

ASSESSMENT OF INJURY OF THE PERITONEUM DURING LAPAROTOMY AND MITIGATION THROUGH USE OF HUMIDIFIED, WARMED CO2

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Introduction: An enigmatic long term complication of abdominal surgery is small bowel obstruction from adhesion formation. It is not well understood why this phenomenon occurs and current methods to prevent this have been unsuccessful. Ambient atmosphere in an operating theatre is understood why this phenomenon occurs and current methods to prevent evidence of peritoneal injury (Primary Outcome). Clinical outcomes were compared between the two groups (Secondary outcomes).

Results: Forty patients were recruited, and samples of peritoneum taken at the beginning and at the end of operations were analyzed and compared. There was a statistically significant increase in the levels of inflammatory cytokines, including IL-1,2,4,5,6,8,10,13,15,17, as well as chemokines MCP-1/ICCL-5/GROa/IP-10 at the end of operation as compared to the beginning of operation (all \( p < 0.05 \)). This was assessed using ELISA/AWB/ IP techniques. There was a statistically significant increase in oxidative damage of the peritoneum as measured by liquid chromatography-mass spectrometry of 3-chlorotyrosine and apoptotic activity in the peritoneum as measured by Caspase-3,7,TUNEL assay. H&E of peritoneum showed significant peritoneal damage at the end of operation. Use of CO\(_2\) mitigated the rise in the level of certain cytokines (IL-2, IL-4), reduced the level of oxidative damage, the level of observed apoptotic activity, and damage of the peritoneum. Clinically, the group receiving CO\(_2\) insufflation had the earlier return of gastrointestinal function (passage of flatus, stool, commencement of diet) and significantly lower rate of postoperative ileus. There was no difference in other clinical outcomes.

Conclusion: Peritoneal injury occurs during open abdominal operations. Use of CO\(_2\) reduces peritoneal injury and improves return of gastrointestinal function postoperatively.

MICRORA MODULATION OF CHEMOSENSITIVITY IN ADRENOCORTICAL CARCINOMA

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Introduction: Adrenocortical carcinoma (ACC) is a rare cancer with a poor prognosis. Patients present late, with advanced disease. Accepted current therapies include surgery with chemotherapy and mitotane. The first international RCT of chemotheraphy/mitotane regimens for advanced ACC showed no increase in overall survival. There is a need for novel treatments for ACC. MicroRNAs (miRNAs) are small non coding RNAs functioning as a promising preservation modality for further clinical implementation; therefore a NMP system was developed and a porcine model utilised to elucidate ideal perfusion conditions.

Methods: (i) A systematic review/meta-analysis was conducted to compare renal transplantation outcomes after MP in comparison to static cold storage (CS), and identify areas for further investigation using animal experimental models. (ii) MP was identified as an ideal opportunity to ameliorate ischemia-reperfusion injury (IRI) through the targeted and direct delivery of pharmacotherapeutics to the organ of interest. Three different IRI targets were therefore compared in a rat model of kidney IRI with intrarenal drug delivery. (iii) Normothermic MP (NMP) was identified as a promising preservation modality for further clinical implementation; therefore a NMP system was developed and a porcine model utilised to elucidate ideal perfusion conditions.

Results: (i) Hypothermic MP (HMP) reduces kidney delayed graft function in comparison to CS (RR 0.77, 95% CI 0.69 −0.87) but does impact long-term outcomes. NMP improves the rate of postoperative ileus and reduces retransplantation rates. (ii) A rat renal IRI model was established, and preliminary evidence indicates intra-renal delivery of CD47 and/or soluble complement receptor 1 may ameliorate IRI. (iii) A clinically translatable NMP system was developed and tested using a porcine kidney donation after circulatory death model. Kidney perfusion appearance and pressures, and urine output can be grossly assessed using this system. Safer perfusion pressures are maintained in a pressure-controlled perfusion system. Perfusion fluid parameters are impacted by perfusion additives and the type of gas mixture utilized for oxygenation.

Conclusions: Renal HMP produces superior immediate graft function, but does not seem to modulate long-term outcomes. Modification of perfusion conditions using NMP in combination with drug(s) targeting IRI may further optimise outcomes. Such a system now needs further testing in the clinical setting.

ADIPOSE DERIVED STEM CELLS AND FAT GRAFTING – A NOVEL THERAPY TO REVERSE THE EFFECTS OF RADIOTHERAPY INDUCED LYMPHEDEMA IN CANCER SURVIVORS

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Introduction: 1/8 females are diagnosed with breast cancer of which 89.4% survive at least five years. The exposure of the chest-wall and axilla...
to radiotherapy (RTX) leads to widespread soft-tissue injury and a 20–40% incidence of secondary lymphedema. Conservative treatments with compression-garments represent an inadequate solution, therefore lymphedema, a disease of cancer survivorship, requires need urgent attention. The presence of lymphedema (static fluid), acts as a culture medium facilitating bacterial growth, worsening lymphatic damage and fibrosis. In order to reverse this injury, it is important to first understand mechanisms of RTX injury at a cellular and molecular level.

Methods: A model of RTX injury was established using a GammaCell® Irradiator to assess RTX induced alterations of lymphatic endothelial cells (LEC) homeostatic functions; viability, proliferation, apoptosis, migration, tube formation models and 3D spheroid models. Next Generation Sequencing was conducted to characterize RTX related molecular alterations. Adipose derived stem cells were harvested from fresh tissue and applied in a model of fat grafting, to test for potential therapeutic benefit in reducing RTX induced LEC injury.

Results/Conclusion: RTX injury results in dynamic functional alterations; global suppression of proliferation, apoptosis, migration, tube formation and sprouting in irradiated cells (p < 0.05). These results may represent protection from sublethal injury allowing cells to harbor latent damage, leading to dysfunctional lymphangiogenesis in RTX tissues. Key RTX mediated molecular alterations were uncovered with genetic sequencing and validated using immunohistochemistry in patient samples. Lastly, our model of fat grafting demonstrated selective amelioration of RTX injury in LEC, not dependent on traditional lymphangiogenic pathways, representing novel therapeutic avenues to improve RTX induced lymphedema.

EFFECTS OF PROGRESSIVE WEIGHT LOSS ON THE METABOLIC SYNDROME IN THE OBESE


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Introduction: Substantial weight loss in the setting of obesity has considerable oncological benefits. Yet some studies have shown improvements in obesity-related comorbidities with more modest weight loss. By closely monitoring patients, we aimed to determine the effects of weight loss on the metabolic syndrome, and determine the target weight loss required for its resolution.

Methods: We performed a prospective observational study of obese participants with metabolic syndrome (ATPIII) who underwent gastric banding. Participants were assessed for all criteria of the metabolic syndrome each month for nine months, after three-monthly follow-up months.

Results: There were 89 participants recruited, with baseline BMI 42.4 ± 6.2 kg and age 48.2 ± 10.7 years. Resolution of the metabolic syndrome occurred in 60 of 89 participants (67%) at 12 months and 60 of 75 participants (80%) at 24 months. The mean weight loss when metabolic syndrome resolved was 10.9 ± 7.7% total body weight loss (TBWL). Hypertension was resolved first, followed by dyslipidemia with achieving 10–12.5% TBWL. Overall, 80% of participants achieved a 5% TBWL at 12 months. Improvement of dyslipidemia was achieved in 73% of participants with an average of 24.7 kg weight loss.

Conclusion: In obese participants, a weight loss target of 10–12.5% TBWL is a reasonable initial goal for metabolic benefit. Further metabolic improvement could be expected with additional weight loss. These findings can help inform weight loss efforts, in counselling patients, determining targets and assessing success of weight loss strategy.

NON-INVASIVE SURVEILLANCE OF ORGAN HEALTH AFTER LIVER TRANSPLANTATION USING DONOR-SPECIFIC CELL-FREE DNA

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Introduction: There is an emerging interest in the use of donor-specific cell-free DNA (dscfDNA) as a non-invasive biomarker of organ health and organ rejection. We have developed a PCR-based approach that readily measures dscfDNA. Using this approach, we evaluated the utility of dscfDNA in two separate cohorts of recipients.

Methods: Deletion/insertion polymorphisms (DIP) were used to distinguish donor- and recipient-specific DNA. Post-transplant dscfDNA was measured using a novel probe-free droplet digital PCR (ddPCR) methodology. In the longitudinal cohort, dscfDNA was serially measured at days 3, 7, 14, 28 and 42 in 27 recipients. In the cross-sectional cohort, dscfDNA was quantified in 16 recipients (>3 months post-transplant) undergoing liver biopsies.

Results: DscfDNA levels were reflective of organ health after liver transplantation. In the recipients who underwent uncomplicated transplantation, dscfDNA markedly reduced at day 7 and remained at low levels from day 14 onwards. Furthermore, dscfDNA was consistently lower in recipients who were clinically stable compared to those who developed biopsy-proven organ rejection.

Conclusion: In this study, we demonstrated a readily performed methodology to measure dscfDNA. We also highlighted the potential of dscfDNA as a non-invasive biomarker of organ health and organ rejection after transplantation.

CLINICAL UTILITY OF A RECTAL CANCER ORGANOID-LYMPHOCYTE BIOBANK

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Introduction: There is a spectrum of response to neoadjuvant chemoradiotherapy for locally advanced rectal cancer, with no reliable test to stratify patients to individual treatment pathway. Furthermore, in those with local or distant recurrence, there are limited therapeutic options to improve their tumour response and overall survival. Promising new therapies such as immunotherapy by check-point inhibition and/or cancer vaccination has emerged to be highly relevant in a subset of colorectal cancer that has high mutational rate, similar to the induction of radiotherapy for rectal cancer. However, the selection of patients for immunotherapy has been limited by current test, with accuracy of predicting response between 20 and 25%. Therefore, the aim of this research is to explore the clinical utility of a novel immune cytotoxic assay utilising rectal cancer organoid with patient-matched tumour infiltrating lymphocytes (TILs).

Methods: This is a prospective observational study. Rectal cancer biopsies were processed to generate rectal cancer organoids and TILs. TILs were Fluorescence-activated Cell Sorting (FACS) to determine the proportion of cytotoxic (CD8+) T cells, a key mediator of tumour lysis. These were then co-cultured for 48 hours and organoid death was measured by calculating the mean fluorescence intensity (MFI) of propidium iodide (a necrotic marker). Assessment of immunotherapy response was performed for anti-PD-1 blockade (a check-point inhibitor) and targeted peptide cancer vaccine.

Results: Seventeen patients were recruited, of which six had pathological complete response (pCR), and eleven non-pCR on histological examination. The MFI for individual patient were grouped according to their pathological response, and an unambiguous difference between pCR and non-pCR at 48 hours is evident, with a mean pCR MFI of 27,982 (95% CI 25,340–30,625) compared with 12,428 (95% CI 9,434–15,423) for non-pCR, reaching clear statistical significance (p < 0.001). Moreover, the assay identified patients that responded to immunotherapy, despite conventional test stating otherwise.

Conclusion: An individualised immune cytotoxic assay measuring the function of cytotoxic TILs has the potential to alter patient management, refining the treatment algorithm for locally advanced rectal cancer. This is also the first platform that has the potential to assist in stratification of different types of immunotherapy.
NEW GENERATION OF BIOPRINTING FOR CARTILAGE REGENERATION
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Introduction: Articular cartilage injuries experienced at an early age lead to the development of osteoarthritis later in life. 3D printing is an exciting new technology to deliver tissue-engineering techniques in orthopaedics. In situ 3D printing has the potential to deliver cutting edge biofabricated scaffolds to regenerate damaged cartilage tissues. The aim of this study was to develop a 3D Bioprinting strategy to create bioscaffolds with high cell viability and good mechanical properties, to finally produce hyaline-like cartilage in vitro.

Methods: We have created a custom-designed hand-held extrusion ink-jet printing device (Biopen) that allows the simultaneous and co-axial extrusion of biomaterial scaffold (Bioink) and cultured cells directly into the defect that needs to be repaired. The co-axial printing allows the cell laden hydrogel Bioink (Adipose Derived Stem Cells (ADSC) in HA-GelMa) to be printed as a core, encapsulated by a photocrosslinkable hydrogel as a protective shell for 3D constructs. In vitro tests of survival (Live-Dead stain), and differentiation toward chondrogenic pathway (Histology; IHC for Collagen type I and II, SOX9, Aggrecan; and RT-PCR) have been performed at multiple time points. Biomechanical indentation tests have been utilized to evaluate physical properties of regenerated cartilage and compared to mature hyaline cartilage.

Results: ADSC printed in HA-GelMa in vitro in a co-axial core/shell distribution remain viable after printing and show marked higher survival when compared to “unstructured” 3D printed cells. The Bioprinted ADSC show a time-dependent increase of expression of SOX 9, Aggrecan and Collagen 2, without the expression of Collagen 1, markers of hyaline-like cartilage. Finally, the bioprinted ADSC express mechanical properties over time indicating cartilage matrix production by chondrocytes.

Conclusion: Cell printing is a feasible means of delivering cells, which retain the capacity to undergo functional differentiation, and is an innovative solution to deliver tissue-engineering techniques to the surgeon for their direct use in vivo. We have identified a 3D printing condition, the co-axial core/shell distribution, that allows increased cells.

MULTIDISCIPLINARY SURVEY OF CURRENT AND FUTURE USE OF EMERGENCY LAPAROTOMY RISK ASSESSMENT SCORES

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Introduction: Emergency Laparotomy (EL) is a common high-risk operation. International efforts are aimed at improving outcomes for EL. Risk prediction is an important part of the management these patients. This study aims to establish current use of and future directions for EL risk prediction scores.

Methods: Trainees and fellows of the Australasian Colleges of Surgery (RACS), Anaesthetia (ANZCA) and Intensive Care Medicine (CICM) were invited to participate in an anonymous survey. The survey was designed after a systematic review of the literature and with input from surgeons and anaesthetists. The survey distributed was an online link via email and by e-newsletters.

Results: Responses were received from 351 clinicians with 45 RACS, 254 ANZCA and 54 CICM members participating. The respondents were mostly specialists (73%) with >10 years’ experience who were involved with caring for 2-3 EL patients per month. RACS members estimated a mortality of 7.5% for EL while ANZCA and CICM estimated 14.3 and 18.7%, respectively (p = 0.002). Risk assessment scores were utilised for EL roughly 30% of the time; this did not differ between specialties. Most respondents used risk assessment preoperatively (RACS 100%, ANZCA 98%, CICM 68%). Respondents “somewhat agreed” that risk assessment scores should only include preoperative variables and intraoperative variables are not necessary for accurate risk prediction. The 3 most common EL risk scores used were (in order): POSSUM, ACS-NSQIP and SORT calculators. The most common reasons for use were familiarity with the score (29%), availability of online calculators or apps (28.4%) and ease of use (19.4%). Less than 5% of responses cited validity of score in EL as a reason for use. RACS and ANZCA members felt that risk assessment was moderately accurate while CICM felt it was only slightly accurate (p < 0.002). The most important outcomes to predict according to respondents were quality of life, followed by 30-day mortality. Functional status and Long-term survival were also viewed as very important outcomes.

Conclusion: Clinicians are preoperatively applying EL risk scores that require intraoperative data and are using them in only approximately 30% of patients. Clinicians need an easy to use risk assessment score that is applicable preoperatively without knowing variables only able to be applied at the time of surgery. Currently there is no such validated scoring system and research is required to develop one.

LONG TERM OUTCOMES FOLLOWING IMPLANTATION OF EMPTY TISSUE ENGINEERED BREAST SCAFFOLDS IN A LARGE ANIMAL MODEL

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Introduction: Breast tissue engineering has the potential to transform breast reconstructive surgery. Current techniques have inherent limitations as they replace tissue rather than regenerating it. Regenerating tissue has the potential to provide a more natural shape and feel to the reconstructed breast. Breast tissue engineering is still in the pre-clinical phase where only a small number of large animal studies have successfully generated soft tissue. However, these studies have not investigated long term outcomes. This study aims to investigate the long term outcome using 3-Dimensional (3-D) printed breast scaffolds to generate larger clinically relevant volumes of soft tissue for breast reconstruction.

Methods: A large animal study was conducted implanting 150 ml biodegradable porous breast scaffolds in 4 immunocompetent minipigs. The scaffolds were manufactured by 3-D printing and made from polycaprolactone. Implants were inserted in subglabular pockets for 8 months. Histological analysis was performed to determine the type, distribution and volume of tissue regeneration.

Results: Soft tissue filled 100% of successfully explanted scaffolds. The tissue type was predominantly fibrous connective tissue. This soft tissue was supported by a neovascularisation. Scaffolds maintained their projection throughout the study period. There was a high wound complication rate (80%) of implant sites.

Conclusion: This study was able to generate large clinically relevant volumes of soft tissue over a long term period using 3-D printed porous breast scaffolds. Further modification to the animal model was made to reduce wound complication rates.

A PROSPECTIVE ANALYSIS OF THE ECONOMIC IMPACT OF PROLONED POSTOPERATIVE ILEUS AFTER ELECTIVE COLORECTAL SURGERY

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Introduction: Prolonged postoperative ileus (PPOI) is a common major complication after abdominal surgery. Retrospective data from the USA suggest PPOI doubles the cost of postoperative inpatient stay. Currently, we lack prospective evidence of the financial burden of PPOI in an Australasian healthcare model. The aim of this study was to determine the economic burden of PPOI for patients undergoing elective colorectal surgery at Auckland City Hospital, using prospective data in an ERAS setting and a standardized PPOI definition.
Methods: Economic data were audited from patients undergoing elective colorectal surgery at Auckland City Hospital between September 2012 and June 2014. Patients were prospectively assessed, using a standardized definition for PPOI. The cost of inpatient stay was analysed with regards to patient demographics, operative and post-operative factors, using the Mann-Whitney U test for continuous data and the chi-squared test for dichotomized data. A multivariate linear regression analysis was performed to determine the cost associated with PPOI when other significant variables were accounted for.

Results: Economic data were attained from 325 patients, of which 88 patients (27%) developed PPOI. The median cost, in NZ dollars, of inpatient stay for patients with PPOI was $27,981 (IQR $21,976) compared to $16,317 (IQR $13,102) in those without PPOI, a 71% increase in cost ($p < 0.005). PPOI also significantly increased healthcare costs across all areas: medical/nursing care, radiology, medication, laboratory costs and allied health ($p < 0.05). The incidence of PPOI was increased in patients who were male (males = 0.021), with lower preoperative albumin ($p = 0.05), who underwent open or converted-to-open surgery ($p < 0.005), and with ASA grade 3 or greater ($p = 0.025). Multivariate analysis showed that PPOI remained a significant factor of healthcare spending ($p < 0.005). The linear regression model found that the expected cost per patient undergoing elective colorectal surgery was $19,137 and PPOI increased this by 35% (95% CI: 21–50%), even when accounting for covariates.

Conclusions: PPOI causes a significant financial burden on the healthcare system. The cost of PPOI is in addition to the fact that these patients have higher rates of complications and are more comorbid. This is the first study to assess the financial impact of PPOI, diagnosed prospectively using a standardized definition in an ERAS setting.

DELIVERY STRATEGIES FOR LAPAROSCOPIC SKILLS TRAINING

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Introduction: Simulation-based education (SBE) has been shown to be effective for surgical skills development. However, simulation activities can be resource and labour intensive. Self-directed SBE sessions have been performed to address these barriers associated with SBE delivery costs and time constraints. This study examined the following questions:

(1) Is self-directed learning effective for achieving proficiency?
(2) Does training in a mobile simulation unit offer any additional benefit?

Methods: A mobile simulation unit (MSU) was deployed to 10 SA and VIC hospitals, completing a total of 17 site visits. Surgical and Gynaecology Trainees, junior doctors and medical students were enrolled and randomised to one of two cohorts: Cohort 1 undertook self-directed learning (SDL); Cohort 2 had formal supervised training, and also undertook SDL. The MSU remained onsite for one week to perform enrolments and allow Cohort 2 training. The SDL period ran for three weeks. Participants recorded the number of task attempts in their logbook. Assessments were performed at baseline (Cohort 1 and 2), at the end of the enrolment and training week (Cohort 2), and at the end of the SDL period (Cohort 1 and 2). Assessment and logbook data were examined to answer the research questions.

Results: 150 participants completed all assessments and provided logbook data: 77 (Cohort 1), and 73 (Cohort 2). Baseline assessment results identified no significant differences between cohorts. Study results identified that:

• Participants in Cohort 2 (MSU + SDL) improved more and with less variability than participants in Cohort 1 (SDL only); this was also achieved over a shorter timeframe.
• SBE should be delivered at their site of employment, individually centred, include a structured training and feedback process, and, be mandatory.
• The biggest barrier to SBE is the ability of participants to access time in which they can undertake training.
• Participants reported that the program met their needs, that it was beneficial to their learning; with 96.1% noting that the course improved confidence in their skills; and that they would continue to train if the simulators remained available.

Conclusions: Results showed that, on average, both cohorts achieved improved scores for all three tasks. Both SDL and MSU training mechanisms resulting in proficient participants with was no statistically significant difference between cohorts.

PATTERNS OF BIOMARKER EXPRESSION PREDICT SURVIVAL AFTER RESECTION IN PANCREATIC CANCER: A RETROSPECTIVE COHORT STUDY AND CLUSTER ANALYSIS

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Introduction: We previously published a systematic review of tumour biomarkers shown individually to have prognostic significance in pancreatic ductal adenocarcinoma (PDAC), and identified a panel of those with the highest level of evidence that could be immunohistochemically detected. These were p53, CKN2A, MUC16, S100A4, FOXC1, EGFR, Mesothelin, smad4, CD24, and UPAR. We aimed to determine whether simultaneous assessment of these proteins would reveal patterns of biomarker expression that better predicted survival outcomes than when these proteins were assessed individually.

Methods: Patients who underwent PDAC resection from 1996 to 2016 were included for analysis. Tissue microarrays (TMA) of formalin fixed paraffin embedded pancreatic tumour specimens were constructed for all patients, stained by immunohistochemistry using antibodies targeted against all 10 proteins, and scored for immunolabelling intensity and percentage of tumour cells stained by two blinded observers. Survival analysis was undertaken by Kaplan–Meier method and differences in survival outcomes were assessed by log rank method. Two-step cluster analysis was performed using biomarkers individually shown to be of prognostic significance to identify patterns of biomarker expression associated with different survival outcomes.

Results: 249 patients were included for analysis. Individual biomarker expression associated with shorter mOS included: S100A4 (18 vs 30 months, p = 0.009), EGFR (13 vs 25 months, p = 0.033), mesothelin (13 vs 26 months, p = 0.001), Ca125 (17 vs 37 months, p < 0.001), and FOXC1 (17 vs 25 months, p = 0.003). Two-step cluster analysis revealed four distinct patterns of biomarker expression, each associated with different survival outcomes: (i) S100A4+ + Ca125+ Mesothelin+ (mOS 12 months); (ii) S100A4+ + Ca125+ Mesothelin- (mOS 17 months); (iii) S100A4+ + Ca125– Mesothelin- (mOS 33 months); (iv) S100A4– + Ca125– Mesothelin– (mOS 40 months); log-rank p < 0.001.

Conclusion: S100A4, Ca125 and Mesothelin immunohistochemistry reveals patterns of biomarker expression that predict survival after resection. The prognostic utility of these biomarkers in tandem is superior than either of these biomarkers assessed individually.

DOES A PATIENT ASSESSMENT AND EDUCATION PROGRAMME DELIVERED BEFORE FIRST CLINIC APPOINTMENT PREDICT WEIGHT LOSS OUT COMES IN A PUBLIC BARIATRIC SURGERY

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Introduction: Our public bariatric service recently developed our model of care requiring patients to participate in a pre-hospital assessment
and education programme prior to first clinical appointment. We sought to test the hypothesis that those patients who lost or maintained weight during our pre-hospital programme would achieve better weight loss following bariatric surgery than those who gained weight during the prehospital programme.

Methods: The first 82 patients who undertook the pre-hospital programme as a part of our pilot have been prospectively followed for 3 years as a part of an ongoing observational cohort study (Alfred HREC 394/12). The primary endpoint was excess weight loss (%EWL) at 36 months from the date of surgery. Excess weight was defined as the weight that a patient was carrying above their ideal body weight (defined as a BMI of 25), and % EWL was defined as the proportion of that excess weight that was lost. Normal data is presented as mean ± SD and was compared using student t-tests; Correlations were performed using Spearman’s test. A p-value of <0.05 was considered significant.

Results: At baseline BMI was 49.8 ± 8.6, there were 62 females and mean age 46.05 years. There were 79 patients who underwent laparoscopic adjustable gastric banding and three patients who underwent a laparoscopic sleeve gastrectomy. The %EWL at 3, 12, 24 and 36 months were: 23.3 ± 13.0% (n = 80); 41.1 ± 20.3% (n = 79); 47.5 ± 25.1% (n = 68) and 45.9 ± 27.3% (n = 64). There were 51 patients who lost or maintained weight during the pre-hospital programme (~3.9 ± 3.5 kg) and 31 patients who gained weight (~3.9 ± 5.6 kg). The weight loss during the programme significantly positively correlated to weight loss at 3 months post-operatively (r = 0.237 p = 0.037). The weight loss at 3 months post-operative significantly positively correlated to weight loss at 12 months (r = 0.524 p = 0.000), 24 months (r = 0.524 p = 0.000) and 36 months (r = 0.36 p = 0.014).

Conclusion: We have previously shown that weight loss 3 months after bariatric surgery is a predictor of long term success. This current study confirms this finding, and also demonstrated that prooperative weight change on our programme correlated positively with weight loss at 3 months. Whilst the preoperative weight change did not predict weight loss at time points beyond 3 months this was possibly due to type II error in this small pilot study. Future studies will measure outcomes from a larger cohort.

**HYPERACTIVE CYCLIC MOTOR ACTIVITY IN THE DISTAL COLON AFTER COLONIC SURGERY**

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Introduction: Recovery after colonic surgery is routinely delayed by disturbed gut motility. It is commonly assumed that colonic motility becomes quiescent during this period, but this hypothesis has not been rigorously evaluated. This study quantified colonic motility through the early post-operative period using high-resolution colonic manometry.

Methods: Fiber-optic high-resolution colonic manometry (36 sensors at 1 cm intervals) was performed continuously throughout the pre-, intra- and post-operative (minimum 16-hours) periods, in the left colon and rectum of patients undergoing right hemicolectomy (n = 8), with comparison to healthy controls (n = 9). Motor events were characterised by pattern, frequency, direction, velocity, amplitude and distance propagated.

Results: Colonic motility became markedly hyperactive in all operated patients, consistently dominated by cyclic motor patterns. Onset of cyclic motor patterns began pre-operatively to a minor extent, occurring with increasing intensity nearer to time of surgery: 12 ± 3% active duration at ≥4-hour pre-operatively vs. 43 ± 7% at <1-hour pre-operatively (p = 0.02); vs. fasted controls 2 ± 4% (p < 0.001). After surgery, cyclic motor patterns increased markedly in extent and intensity, becoming nearly continuous (94 ± 3% active duration; p = 0.001), with peak frequency 2–4 cycles/min in the sigmoid. This post-operative cyclic pattern was substantially more prominent than in non-operative controls, including in the fed-state (27 ± 21% active duration; p < 0.001), also showing faster velocity (p < 0.01).

Conclusions: Distal gut motility becomes markedly hyperactive with right-sided colonic surgery, dominated by cyclic motor patterns. This hyperactivity likely represents a novel pathophysiological aspect of the surgical stress response. Hyperactive motility may contribute to gut dysfunction after surgery, potentially offering a new therapeutic target to enhance recovery. Supported by the RACS James Ramsay Project Grant.

**SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF SURGICAL MANAGEMENT OF GASTRO-oesophageal REFLUX DISEASE IN ADULTS**

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Introduction: Proton pump inhibitors (PPI) are the mainstay of treatment for gastro-oesophageal reflux disease (GORD), but are associated with potential side effects and ongoing cost. Anti-reflux surgery is cost-effective, and is preferred by many patients. A total (360 degree or Nissen) fundoplication is the traditional procedure, but other variations including anterior and posterior partial fundoplications are also commonly performed, with the aim of achieving durable reflux control with minimal dysphagia. Many randomised controlled trials (RCTs) and some pairwise meta-analyses have compared some of these procedures but there is still uncertainty about which, if any, is superior. Network meta-analysis (NMA) allows for multiple simultaneous comparisons, and robust synthesis of the available evidence in these situations. An NMA comparing all anti-reflux procedures was performed, to identify which has the most favourable outcomes at short (1 year), medium (5 years) and long-term (10 or more years) follow-up.

Methods: Article databases were systematically searched for all eligible RCTs. Primary outcomes were quality of life measures and dysphagia. Secondary outcomes included reflux symptoms, pH studies and complications. NMA was performed using Stata 13.1 (College Station, Texas) analysing data at four follow-up time-points separately, with PPI allocated as the reference treatment.

Results: 51 RCTs were included, involving 5357 patients, and 14 different treatments. Posterior partial fundoplication (PPF) ranked best in terms of reflux symptoms, and caused less dysphagia compared to most other interventions including Nissen fundoplication. This result was consistent across all time-points and outcome measures.

Conclusions: In adults with GORD, PPF provides the best balance of long-term, durable reflux control with less dysphagia, compared to other procedures, and medical therapy. PPI should be considered the gold standard intervention for the surgical management of GORD in adults.

**SURGEON REFLECTION AFTER A PATIENT’S DEATH – A QUALITATIVE STUDY UTILISING MORTALITY AUDIT DATA**

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Introduction: Surgical deaths in Australia require the treating surgeon to document the event via a standard report. A section of this report invites surgeons to reflect on changes to management they would initiate with retrospect. Retrospect provides a unique perspective for individuals and teams to analyse decision making and reflect on performance. We analysed these reflections and categorised them according to surgeon experience level, surgical diagnosis and admission type in an effort to elucidate insight into surgical decision making.

Methods: This audit based cross-sectional study involves patients who died in-hospital under the care of General Surgeons in Queensland, Australia between July 2007 and December 2016. Retrospective surgeon statements were analysed and categorised qualitatively.

Results: We identified 531 of 3,073 (29%) General Surgeons who indicated they would manage their patient differently in retrospect. Statements were categorised into operative decisions, changes to ward based clinical decisions, communication considerations, ceiling of care decisions and technical operative decisions. More experienced Surgeons were more likely to make retrospective changes to an operative decision. Surgeons whose patients were admitted with small bowel obstruction and mesenteric

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ischaemia were more likely to indicate they would operate sooner in retrospect. Surgeons whose patients had undergone elective operations were more likely to indicate they would not have operated with hindsight.

Conclusions: The methodology of this study is unique in utilising large-scale mortality audit data to gain insight into the reflective opinions of surgeons. This qualitative study has identified decision making around operative management as the most common area of reflective consideration in a number of different situations. Our findings support existing literature in finding the decision to operate, or not, is difficult.

IT WAS POSSIBLE TO CONDUCT, FOR THE FIRST TIME, A LONGITUDINAL GETTING TO GRIPS – A LONGITUDINAL CLINICAL MODEL TO STUDY THORACIC DUCT LYMPH COMPOSITION

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Introduction: Multiple organ dysfunction syndrome (MODS) is the commonest cause of death from critical illness in Intensive Care. Enteral feeding is a central tenant of supportive care in intensive care. The lipid portion of enteran nutrition is absorbed through the gut lymphatics. Experimental evidence indicates that toxic changes in gut lymph draining via the thoracic duct (TD) in these settings drives systemic inflammation and MODS. Translating these findings to the clinical setting has been prevented by the inability to readily access and study TD lymph.

Methods: The TD was cannulated with a ureteric catheter, ligated distally and exteriorised during thoracotomy phase of Ivor Lewis oesophagogastrectomy (HDEC Ethics 12/NTB/67). Enteral feeding was introduced step-wise from the second post-operative day. Every 12 hours TD lymph and peripheral plasma were sampled on ice, centrifuged (1900g, 3000g, both for 10 minutes at 4°C), supernatant aliquoted and stored at −80°C. Standard biochemistry, gut hormones (amylin, c-peptide, ghrelin, glucagon, insulin, leptin), enzyme-linked immunosorbent assays of gut injury marker (intestinal fatty acid binding protein, iFABP) and pro-inflammatory cytokines assays (interleukin-6, IL-6 and tissue necrosis factor alpha, TNF-α) were performed comparing lymph and plasma.

Results: The TD cannulation was successful in 3 of 4 cases and was sampled for 3–5 days after surgery. As expected total protein (55–56 g/L vs 29–34 g/L), albumin (34–38 g/L vs 14–22 g/L), HDL (2.5–4.3 fold), LDL (5.2–12.8 fold) and cholesterol (2.3–3.1 fold) were all consistently higher in plasma than lymph, while triglyceride (3.7–3.8 fold) and lipase (2.7–7.7 fold) were higher in lymph than plasma. The novel findings were that markers of gut injury, iFABP (3 fold) and pro-inflammatory cytokines, IL-6 (10–40 fold) and TNF-α (3–5 fold) were elevated in lymph compared with plasma, with a second peak following the commencement of enteral feeding.

Conclusions: It was possible to conduct, for the first time, a longitudinal study of TD lymph composition in patients after major surgery. The compositional changes are consistent with TD lymph driving inflammation, and suggests that a less invasive approach to TD sampling and drainage might offer valuable insights into the pathogenesis of MODS.

THE UTILITY OF A PREDICTIVE MODEL TO AID IN THE MANAGEMENT OF INTACT ABDOMINAL AORTIC ANEURYSMS

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Introduction: Predicting outcomes prior to elective abdominal aortic aneurysm repair (AAA) requires critical decision-making, as the treatment offered is a prophylactic procedure to prevent death from a ruptured AAA. The aim of this work was to develop and validate a model that may predict outcomes for patients with an AAA and hence aid in clinical decision-making.

Methods: A discrete event simulation (DES) model was built to simulate the natural history of a patient with an AAA and to predict the 30-day, 2–5 year survival of patients undergoing treatment and surveillance. The input parameters of AAA behaviour an impact of comorbidities on survival were derived from the published literature and the national life-tables. The model was externally validated using a cohort of patients that underwent AAA repair (n = 320) and a cohort of patients undergoing that were reviewed in a small AAA surveillance clinic (n = 376). All patients had completed at least 5-year follow-up.

Results: The model was run three times for each dataset to test the reproducibility of the model prediction and the standard deviation was less than 1% indicating excellent reproducibility. The observed 30-day mortality for the patients undergoing AAA repair was 9/320 (2.8%) and the expected mortality was 3.8%, c-statistic 0.87 (95% CI: 0.75–1.0). Of the 21 deaths in the first year after AAA repair, the model predicted that 10 deaths could have been avoided if AAA repair had not been performed. The c-statistic for the predicted 2–5 year survival ranged from 0.68 to 0.71 for the repaired AAA cohort and 0.69 to 0.73 for patients with a small AAA on surveillance.

Conclusion: The AAA clinical decision tool has the ability to accurately predict the 5-year survival of patients with an AAA. This tool can be used during clinical decision making to better inform clinicians and patients of long-term outcomes. Further validation studies in a wider AAA population are required to test the broader clinical utility of this AAA clinical decision tool.

A PROTEOMIC APPROACH TO BIOMARKER DISCOVERY IN PATIENTS WITH PANCREATIC DUCTAL ADENOCARCINOMA USING A NOVEL MASS SPECTROMETRY TECHNIQUE

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Introduction: The poor survival of pancreatic ductal adenocarcinoma (PDAC) is largely attributable to late diagnosis and poor selection of patients for surgery. There is a therefore significant need for accurate diagnostic and prognostic biomarkers in PDAC. Here, we present a proteomic approach due tumour biomarker discovery using a novel high-throughput technique (Sequential Windowed Acquisition of All Theoretical Fragment Ion Mass Spectra; SWATH-MS). We aimed to identify proteins differentially expressed by PDAC compared with adjacent normal pancreatic tissue, and identify uniquely secreted upregulated proteins in PDAC for future analysis in plasma.

Methods: Patients undergoing pancreatic resection for histologically proven PDAC were recruited from June 2016 to June 2017 at our institution. A portion of tumour and adjacent normal pancreas were obtained from each resected specimen. Pooled proteins from all patients were analysed with LC-MS/MS to generate a spectral library of all quantifiable proteins. Individual peptides in each sample were then quantified with SWATH-MS. The Ingenuity Pathway Analysis Platform (QIAGEN, Redwood City, USA) was used to characterise canonical pathways, upstream regulators, and to identify candidate proteins for future analysis in plasma.

Results: Thirteen patients with histologically proven PDAC were included for analysis. 4009 proteins were identified in all samples. Eighty proteins were identified as significantly upregulated in PDAC (log2 ratio > 1, p < 0.05). Those with the greatest fold-change were S100P (log2 ratio 3.35), p = 0.0006, CEAMS (log2 ratio 2.121, p = 0.0042), trefoil factor (log2 ratio 2.031, p = 0.0021), and cathepsin E (log2 ratio 1.807, p = 0.0047). Seven proteins were identified as unique to PDAC and secreted in plasma with a log2 ratio > 1 and p < 0.05. Canonical pathways most significantly upregulated in PDAC included integrin signalling, actin cytoskeleton signalling, and remodelling of epithelial adherens junctions. Several upstream regulators were identified in PDAC including: TGFβ1, interferon-gamma, tumour necrosis factor, ERK and STAT.
INVESTIGATING THE MECHANISMS INVOLVED IN CARDIOVASCULAR MORBIDITY FOLLOWING NON-SEVERE BURN INJURY

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Introduction: Recently published research correlating animal, patient and West Australian population data strongly suggests that non-severe burn injury (NSBI) leads to long-term cardiovascular morbidity in some patients. The cause of this is unknown and is likely to be multi-factorial.

Aim: Identify the mechanisms involved in cardiovascular dysfunction following NSBI.

Hypothesis: Vascular endothelial dysfunction, platelet up-regulation and dysbiosis of the gut microbiome contribute to cardiovascular morbidity post NSBI.

Methods: (1) Using a validated rodent (C57Bl/6 female mice) model of NSBI: (i) Endothelial relaxation was analysed using 2 mm segments of abdominal aorta. Vessels were mounted on a small vessel wire myograph system 620M (DMT, Denmark), preconstricted using phenylephrine and then response to acetylcholine (endothelial dependent relaxation) and sodium nitroprusside (endothelial independent relaxation) was measured, percentage endothelial relaxation was then calculated. (ii) Following cardiac venepuncture platelet analysis was performed using flow cytometry, laser scatter and CD61 expression to identify platelets. CD62P expression was used as a marker of activation and or granule exocytosis. Mice were placed on normal or high fat diet. Day 7 and Day 28 timepoints were used.

(2) Short Chain Fatty Acid Analysis was performed on plasma samples from paediatric patients following NSBI. Levels of Acetate, Propionate or Butyrate were compared between NSBI and control groups.

Statistical analysis was performed using SPSS and graphpad prism statistical software.

Results: In the murine model of NSBI provisional data suggests endothelial dysfunction in the high fat diet group only. Provisional murine platelet analysis shows statistically significant up-regulation of platelets at day 28 post NSBI. In paediatric plasma samples there is no statistically significant difference in acetate, propionate or butyrate levels, however there is a considerable standard deviation, therefore analysis of more samples is required and will be presented.

Conclusion: There is Endothelial dysfunction in the murine model of NSBI when the mice are fed high fat diet, highlighting the impact of this as a pre-existing independent risk factor in burns patients. Platelet up-regulation is seen in mice following a NSBI, platelet up regulation is associated with acute coronary syndrome in patients. Further paediatric plasma sample short chain fatty acid analysis is required.

ENGAGING JUNIOR DOCTORS IN TEACHING THROUGH OPEN-SOURCE CURRICULUM PACKS

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Introduction: Teaching of medical students by junior medical staff (a form of “near-peer” teaching), is a teaching style which presents medical students with unique insight into the day-to-day workings of the intern or resident. Junior doctors however may be discouraged from teaching due to a variety of factors including time constraints, lack of institutional support, lack of training, and unfamiliarity with certain topics.

Method: A new curriculum was developed focusing both on the strengths of junior medical officer knowledge and subject matter relevant to the final year medical student. Ten curriculum packs were created containing a syllabus, exercises, and scenarios for junior doctors to access and use in on-the-spot teaching. The packs are open source and available online free of charge worldwide. The packs were trialled in final year medical students by junior doctors – of which most had no training in teaching.

Results: 30 sessions were conducted over eighteen months by over twenty junior medical officers at two hospitals in the Central Coast, Australia. From the 197 feedback forms received, students found the junior doctor led sessions relevant (194, 98.4%), approachable (196, 99.5%), engaging (192, 97.46%), unique (191, 97.0%) and leading to an increase of knowledge (188, 95.43%). Free-text strengths include praise for friendly and non-confrontational sessions, relevance, and use of clinical scenarios. Free-text weaknesses include criticism of longer sessions, not enough clinical scenarios within those sessions and a desire for more tutorials to be held.

Discussion: This trial teaching programme provides a promising and effective way to engage junior medical officers in teaching with minimal capital and logistical burden. The authors look forward to expanding and refining its curriculum and engaging international stakeholders to trial the programme at their own institutions.

EXPLORING THE IMMUNE LANDSCAPE AND ASSESSING THE ROLE OF IMMUNOTHERAPY IN COLORECTAL PERITONEAL METASTASES

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Introduction: Colorectal cancer is the third most common cancer worldwide. Up to 25% of patients have disease that spreads to the peritoneum, which leads to a very poor prognosis. Systemic chemotherapy offers modest improvement in survival. Aggressive cyto-reductive surgery and hyperthermic intraperitoneal chemotherapy is effective in very selected patients. However, the majority of patients are not suitable surgical candidates. The immune response in peritoneal metastases has not been assessed previously. Immunotherapy, while effective in other cancers, has an undefined role in peritoneal disease.

Methods: Fresh tumour tissue from colorectal peritoneal metastases was used for flow cytometry analysis to evaluate immune cell infiltration. Tissue was further processed to develop robust organoid models. Simultaneous patient matched tumour infiltrative lymphocytes (TILs) were cultured and enriched with interleukin-2 (IL-2). Once organoids were robust and replenishable, they were co-cultured with various concentrations of TILs to assess the cytotoxic ability of the lymphocytes. They were further cultured with TILs with the addition of an anti PD-1 antibody.

Results: Flow cytometry revealed a large CD45 population of mainly T cells. There was an even mix of CD4 and cytotoxic CD8 cells. However, there were unexpectedly high T-regulatory cells, comprising up to 15% of CD4 cells. PD-1 expression on T cells, whilst variable, was up to 45% suggesting a possible role for anti PD-1 antibody therapy. Co-culture with organoids, TILs and PD-1 antibodies demonstrated organoid killing increased significantly with the addition of anti PD-1 antibody.

Conclusions: This early pre-clinical data demonstrates a potential role for immunotherapy in the setting of peritoneal disease. These early results need to be expanded with a larger cohort, and validated in an in-vivo setting.

TECHNIQUE TO RECREATE THE 3D MORPHOLOGY OF THE HUMAN TYMpanic MEMBRANE FOR RECONSTRUCTIVE TYMpanoplasty Graft Design: A Validation Study

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Introduction: 3D printing has recently gained significant interest for its ability to rapidly prototype complex geometries, spurring innovation in tissue engineering, surgical prostheses and regenerative medicine. Current tympanoplasty techniques reconstruct large tympanic membrane

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In renal hyperparathyroidism, patients with TM perforations and tissue grafts, manually fashioned from autologous material, often experience prolonged operative times due to the need for harvesting and customising TM grafts. Unfortunately, up to 31% of TM grafts fail to heal, and graft migration during the healing process can result in a worsened post-operative conductive hearing loss. Crucial intra-operative time is spent harvesting and fashioning customised TM grafts, increasing length of surgery and donor site morbidity. The 3D shape and fit of TM grafts influence graft uptake, surgical ease and hearing outcomes in reconstructive tympanoplasty. We describe a novel technique to reproduce the 3D complex shape of the TM to facilitate the accurate 3D printing of TM grafts.

**Methods:** Computer-aided design (CAD) was used to model the custom 3D shape of an ex-vivo human cadaveric TM. The CAD model was compared to silicone cast impressions of the cadaveric TM, which acted as reference shapes, in order to assess for model accuracy, precision and 3D shape-similarity. The CAD model and averaged silicone cast impressions were compared using point-cloud analysis software.

**Results:** The CAD model displayed remarkable shape-similarity to the silicone impressions from the ex-vivo human cadaveric TM. Silicone cast impressions did not adhere to the TM in our technique, or cause any perforation or canal wall damage. The CAD model demonstrated an averaged cloud-to-mesh signed distance of 0.019 mm with a standard deviation of 0.11 mm across the scalar field from the averaged silicone cast impressions. Greatest deviation from the averaged silicone impression occurred at the umbo and mid-malleus region. A 3D-printed TM-shaped graft designed from the CAD model was easy to insert and adapted well to the lateral and medial aspects of the ex-vivo human cadaveric TM.

**Conclusions:** Our novel CAD-based approach to modelling the 3D shape of the TM, holds significant promise for improving the surgical ease, graft uptake and hearing outcomes in reconstructive tympanoplasty with 3D-printed TM grafts. Further research will be performed to validate this modelling approach in more ex-vivo cadaver samples and in-vivo human volunteers.

**LONGITUDINAL OUTCOMES OF PARATHYROIDECTOMY WITH AND WITHOUT AUTO-TRANSPLANT IN RENAL HYPERPARATHYROIDISM: A SINGLE SURGEONS’ EXPERIENCE**

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Introduction: Surgeons have debated for the last 35 years on the most optimal technique for operative management of secondary hyperparathyroidism. Subtotal parathyroidectomy (SPTX), total parathyroidectomy with autotransplant (TPTX + AT), and total parathyroidectomy without autotransplant (TPTX) have been described, with varying results. The aim of this study was to compare a single surgeon’s longitudinal outcomes of TPTX + AT and TPTX.

**Methods:** We reviewed 68 patients over 48 months since operation, of which 54 patients had TPTX + AT, and 16 patients had TPTX. Parathyroid hormone level (PTH) was analysed between two time periods: group (a) 10/05/2001–20/11/2006; and group (b) 21/11/2006–12/05/2011, due to different PTH assays utilized in our institution. Biochemical markers were serially analysed. Recurrence of hyperparathyroidism, as well as re-operative rates over the postoperative course were tabulated and compared.

**Results:** The postoperative trend of PTH remained largely comparable, with a gradual trend towards an elevation of PTH values between TPTX + AT and TPTX. In group (a), peak PTH was achieved at 48 months in both the TPTX + AT group (6.03 ± 9.08 pmol/L; 95% CI 3.38–6.68) and TPTX group (9.45 ± 10.96 pmol/L; 95% CI 2.29–16.61; p ≤ 0.05). In group (b), peak PTH was achieved at 48 months in the TPTX + AT group (18.61 ± 13.30 pmol/L; 95% CI 12.29–24.93) and at 42 months in the TPTX group (8.77 ± 6.45 pmol/L; 95% CI 3.11–14.43; p ≤ 0.05). 29.63% of the TPTX + AT and 18.75% of TPTX were associated with elevated PTH and hyperparathyroidism during follow-up beyond 1 month. Both study groups maintained corrected calcium levels within normal range during follow-up. 3.70% of patients who had TPTX + AT had hyperplasia of the autotransplant requiring excision after 35 and 66 months since initial operation.

**Conclusion:** Long term PTH and calcium outcomes in renal hyperparathyroidism appeared to be similar between TPTX + AT and TPTX groups. Recurrent hyperparathyroidism occurred slightly higher in the TPTX + AT group. In TPTX, it is thought that “rests” of parathyroid cells potentially deposited during embryological descent undergo hyperplasia from chronic uraemic stimulus from chronic renal failure. These cells are probably sufficient to secrete PTH and maintain normal serum calcium levels in the absence of parathyroid glands. Thus, TPTX may provide a safe and viable surgical option with good long term outcomes, without the risk of permanent hypocalcaemia and recurrence.