Association of Surgeons of Great Britain and Ireland

Education & Innovation

2014 INTERNATIONAL SURGICAL CONGRESS

HARROGATE

Moynihan Prize Papers
ABSTRACTS

(7 minute presentation + 3 minutes discussion)

1.45pm to 3.00pm
Thursday 1st May 2014
Main Auditorium
Harrogate International Centre
(Congress Session T6A)

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2014 Moynihan Prize Papers – Abstract: 0066

RANDOMISED DOUBLE-BLINDED TRIAL COMPARING CUTTING DIATHERMY *VERSUS* SCALPEL FOR SKIN INCISIONS: IS THERE A DIFFERENCE IN COSMETIC OUTCOME?

L N F Aird [1]*, S G Bristol [2], P T Phang [3], M J Raval [3], C J Brown [3]

[1] University of British Columbia Division of General Surgery, Vancouver
[2] University of British Columbia Division of Plastic Surgery, Vancouver
[3] Department of Surgery, St Paul's Hospital, Vancouver

Aims: Controversy exists whether cutting diathermy for skin incisions leads to a cosmetically inferior scar. We compared cosmetic outcomes between skin incisions created with cutting diathermy and scalpel. Furthermore, we compared wound infection rates and post-operative incisional pain.

Methods: A randomized, double-blinded trial comparing these two methods in patients undergoing bowel resection was conducted. The primary outcome was wound cosmesis at 6 months after surgery, assessed independently by a plastic surgeon and a research associate using validated scar assessment tools: the Vancouver Scar Scale (VSS) and the Patient Observer Scar Assessment Scale (POSAS). Patients also subjectively evaluated their own scars using POSAS. Wound infections within 30 days were recorded, and 5-day post-operative incision pain scores were evaluated with a Visual Analogue Scale (VAS). Student's *t*-test and Fisher's exact test were used for comparisons of continuous and categorical data, respectively.

Results: Between March 2012 and August 2013, 66 patients were randomized to cutting diathermy (n=31) or scalpel (n=35). There was no significant difference in patient characteristics. At 6 months there was no significant difference in cosmesis, as measured by VSS score (4.9 ± 2.6 in the diathermy group *versus* 5.0 ± 1.9 in the scalpel group, p=0.84) or objective POSAS score (19.2 ± 8.0 *versus* 20.0 ± 7.4, p=0.68). There was also no difference in the subjective, patient-reported POSAS score (20.2 ± 12.1 *versus* 21.3 ± 10.4, p=0.73). Additionally, there was no significant difference in wound infection rates between groups (16.7% *versus 16*.1%, p=1.00). Post-operative day 1 VAS scores were significantly lower in the diathermy group (1.68 *versus* 3.13, p=0.018), while at days 2-5 they were not significantly different.

Conclusions: Cutting diathermy is a cosmetically acceptable modality for abdominal skin incisions. Additionally, there is no increased risk of wound infection and it may convey some benefit in early post-operative wound pain.

2014 Moynihan Prize Papers – Abstract: 0281

THE THROMBIN CLOTTING PATHWAY IS UPREGULATED IN THE STROMA OF PRE-INVASIVE BREAST CANCER AND FURTHER UPREGULATED IN AGGRESSIVE INVASIVE BREAST CANCER PHENOTYPES

H Shaker [1]*, N J Bundred [1], H Albadry [2], S L Nicholson [2], C C Kirwan [1]

[1] The University of Manchester, Manchester Academic Health Science Centre
[2] Department of Histopathology, University Hospital of South Manchester

Background: The thrombin (extrinsic) clotting pathway is upregulated in cancer. Thrombin pathway factors Thrombin and Tissue Factor (TF) promote tumour progression through protease activated receptors PAR1 and PAR2 respectively. Breast cancer (BC) consists of distinct phenotypes, of which ER-ve and HER2+ve have worse prognosis.

Aim: Determine if tumour expression (epithelial and stromal) of a procoagulant phenotype is associated with aggressive BC phenotypes.

Methods: Tumour expression of TF, thrombin, PAR1 and PAR2 was determined by IHC in two cohorts. **Prospective cohort study**: Early invasive BC (n=182), DCIS (n=35) and normal breast tissue (n=93). **Post-hoc analysis of archived tissue**: Invasive BCs (n=84) from 2001/02 study with median follow-up of 69 months. Expression was correlated with tumour grade, proliferation (Ki67 expression), ER and HER2 status (both cohorts), survival and recurrence (archived tissue cohort).

Results: Prospective study: Epithelium: Thrombin ($p<0.01$) and its receptor PAR1 ($p=0.03$) were increased in invasive BC compared to DCIS and normal. In invasive BC, TF was associated with ER+ve ($p<0.01$) and low tumour grade ($p=0.02$). Stroma: TF was increased in DCIS vs control and further increased in cancer vs DCIS ($p<0.01$). Thrombin, PAR1 and PAR2 were increased in cancer and DCIS vs normal ($p<0.01$). In invasive BC, stromal TF and thrombin was increased in HER2+ve ($p<0.01$) and correlated with increasing Ki67 ($p<0.001$). Stromal TF was increased in ER-ve ($p=0.02$) and high grade cancer ($p<0.001$). Stromal PAR1 and PAR2 correlated with KI67 and were increased in high grade cancer ($p<0.01$, all). PAR1 was increased in ER-ve ($p<0.01$) and PAR2 in HER2 +ve ($p<0.01$). **Archived tissue**: Stroma: As with first study, PAR1 was increased in ER-ve ($p<0.01$) and PAR2 in HER2+ve ($p<0.01$). PAR1 stromal expression correlated with reduced overall ($p=0.02$) and recurrence free ($p=0.07$) survival.

Conclusions: Stromal upregulation of thrombin pathway in DCIS implies cancer-stromal communication at the pre-invasive stage. Stromal (not epithelial) thrombin pathway upregulation is associated with aggressive invasive BC phenotypes and reduced survival. The thrombin pathway may provide a novel therapeutic target, particularly in ER-ve, HER2+ve BC.

2014 Moynihan Prize Papers – Abstract: 0637

NATIONAL COHORT STUDY AND PROPENSITY SCORE MATCHED ANALYSIS INVESTIGATING DAY OF THE WEEK OPERATING AND 30-DAY MORTALITY FOLLOWING ELECTIVE COLORECTAL RESECTIONS

R S Vohra [1]*, T Pinkney [1], F Evison [2], I Begaj [2], D G Morton [1]

[1] Academic Department of Surgery, University of Birmingham, Birmingham
[2] Health Informatics Department, University of Birmingham, Birmingham

Aims: The studies describing variations in outcomes following elective operations performed on Fridays have failed to adjust for selection biases that may account for operations taking place on different days of the week. We investigated this and the effect on 30-day mortality in patients undergoing elective colorectal resections performed between Mondays and Fridays.

Methods: Using Hospital Episode Statistics, we identified 204,669 elective colorectal resections performed in England from 2001-2011. Using propensity scores, patients were matched in a one-to-one ratio based on the risks that lead to elective operations taking place on Fridays with those performed on other days (n=55,810). Odds of death were calculated.

Results: Despite a 29.6% rise in the total numbers colorectal resections performed over the 10 years, 25.9% fewer were performed on Fridays compared to Mondays (13.6% vs 18.4%, p<0.001). Patients operated on Fridays were more deprived (deprivation score=1, 17.1% vs. 16.0%, p<0.001), had a greater proportion of benign diagnoses (23.3% vs 21.9%, p<0.001) and had a higher crude 30-day mortality (3.3% vs 2.8%, p<0.001) compared to Mondays to Thursdays. Using these and other selected preoperative factors, propensity scores were used to match colorectal patients operated on Friday with patients from other days of the week. Despite this, the risk of 30-day mortality of operations performed on Fridays was still higher compared to Mondays (1.30, 95%CI 1.09-1.54, p<0.001).

Conclusions: The patients operated on Friday have significant adverse preoperative risk factors that might account of the additional mortality seen in this and other studies. This suggests the 'weekend effect' may reflect other, undetermined patient factors, rather than publicised hospital variables. However, attempts to control for these did not eradicate the apparent increased early postoperative mortality.

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2014 Moynihan Prize Papers – Abstract: 0760

FIRST IN MAN QUALITY ASSESSMENT OF HUMAN KIDNEYS USING *EX-VIVO* NORMOTHERMIC PERFUSION

A Barlow*, S Hosgood, J Hunter, M L Nicholson

University Hospitals of Leicester

Background: The suitability of kidneys for transplantation is currently assessed primarily using donor characteristics. Even with the addition of other measures such as macroscopic appearance, histological examination and hypothermic perfusion parameters assessment of viability is difficult. Because of this uncertainty, about 15% of donated kidneys are declined for transplantation. Ex vivo normothermic perfusion (EVNP) allows a functional assessment of kidney viability and may allow more accurate prediction of graft outcome.

Methods: Sixty five human kidneys deemed unsuitable for transplantation after retrieval underwent 60 minutes of EVNP with an oxygenated red blood cell based solution at 36.0°C. Renal blood flow and urine output were the primary functional parameters. Receiver operating characteristic (ROC) curves were used to identify thresholds of these variables for kidney viability. These thresholds, along with macroscopic appearance, were incorporated into a viability score (renal blood flow <63mls/min = 1; urine output <50ml/hr = 1; macroscopic assessment of perfusion: good = 1, patchy = 2, poor = 3), with a possible total score of 1 to 5.

Results: Of the 65 discarded kidneys 20 had a viability score of 1 (high predicted viability), 14 scored 2, 13 scored 3, 5 scored 4 and 13 had a viability score of 5. When the viability score was applied to a series of 36 marginal kidneys transplanted after EVNP, 26 had a viability score of 1-2, 10 scored 3-4 and none scored 5. The delayed graft function rate was 3.8% in kidneys scoring 1-2 and 30% in those scoring 3-4 (P = 0.056). eGFR was significant lower in kidneys with a score of 2-3 up to 3 months post-transplant compared to those scoring 0-1 (35 ± 11 vs 53 ± 17mls/min; P = 0.005). On this basis, of the 65 discarded transplant kidneys, 52 were deemed viable and suitable for transplantation.

Conclusions: Functional parameters and visual assessment of a kidney during 60 minutes of EVNP may be used to reliably assess graft quality. The technique may be used to increase transplant rates by decreasing the number of discarded kidneys, whilst safeguarding against primary non function.

2014 Moynihan Prize Papers – Abstract: 0804

SIP1 INDUCED ACTIVATION OF NUCLEOTIDE EXCISION DNA REPAIR (NER) PATHWAY MEDIATES CHEMORESISTANCE IN COLORECTAL CANCER (CRC)

R Sreekumar *, A Patel, A Mirnezami, E Sayan, J N Primrose

Southampton University, Cancer Sciences Division, Southampton

Aims: Epithelial to mesenchymal transition (EMT) is a conserved cellular program with a critical role in cancer progression and recurrence. The cardinal features of EMT include E-Cadherin down regulation, acquisition of a metastatic phenotype and modulation of chemosensitivity through poorly understood mechanisms. Cancer recurrence after surgical resection is the primary cause of morbidity and mortality in CRC and chemoresistance is a major obstacle in improving survival in patients with stage 4 disease. Here, we identify SIP1 as an inducer of EMT in CRC, demonstrate for the first time its role in mediating chemoresistance, dissect the cellular pathways contributing to impaired response to Oxaliplatin in-vitro and test our results in an orthotopic murine model.

Methods: 157 consecutive patients undergoing surgical resection for CRC were prospectively evaluated for SIP1 expression. IHC was scored by two independent pathologists and survival analysis undertaken using Kaplan–Meier and Cox proportional hazard regression. SIP1-induced resistance to Oxaliplatin was studied using an inducible in-vitro cell model (DLD-SIP1) and apoptosis assessed by Western blotting and flow cytometry. Transcriptomic expression profiling was conducted and analysed for deregulated genes. In-vivo evaluation of tumour development and drug response were undertaken in an orthotopic murine model with in vivo tumour imaging.

Results: SIP1 overexpression in DLD-SIP1 cells induced E-Cadherin down regulation and Vimentin up regulation, hallmarks of EMT. IHC analysis of SIP1 expression in 157 CRC patients revealed SIP1 positivity in 61%. SIP1 was an independent prognostic marker predictive of Cancer specific survival, Disease free survival and poor response to chemotherapy. In-vitro, SIP1 expressing CRC cells treated with Oxaliplatin were more resistant to apoptosis. To identify downstream genes involved in SIP1-induced Oxaliplatin resistance, expression profiling was conducted and nucleotide excision repair (NER) genes, ERCC1 and ERCC4, identified as up regulated. We show overexpression of ERCC1/ERCC4 in this manner promotes resistance to Oxaliplatin in-vitro, and use an in-vivo orthotopic mouse model to evaluate the role of increased NER activity in SIP1-induced chemoresistance in CRC.

Conclusions: Our results demonstrate SIP1 induced EMT directly up regulated NER activity in CRC, thus promoting resistance to Oxaliplatin. Targeted inhibitors of NER genes, may provide an effective adjunct to current treatment regimens in metastatic CRC.

2014 Moynihan Prize Papers – Abstract: 0926

DEVELOPING MODEL SYSTEMS TO UNDERSTAND THE FUNCTIONAL AND CLINICAL SIGNIFICANCE OF SOMATIC GENETIC VARIATIONS IN OESOPHAGEAL CANCER

A Cowie [1]*, E Garcia [1], A Hayden [1], T Underwood [2], on behalf of the OCCAMS Consortium

[1] Cancer Sciences Unit, University of Southampton
[2] OCCAMS Consortium, UK Clinical Research Network, UK

Aims: The Oesophageal International Cancer Genome Consortium (ICGC) project is currently using whole genome sequencing (WGS) to define the genetic landscape of oesophageal adenocarcinoma (EAC). New biological tools are required to understand the functional and clinical significance of these genetic events. We describe the generation and authentication of a novel EAC cell line for functional validation of somatic variants discovered by WGS in a tumour from a 55-year-old male (pT4N3M0) who died from disease recurrence 7 months after neo-adjuvant chemotherapy and oesophagectomy.

Methods: The MFD-1 cell line was expanded directly from a resected EAC specimen without recombinant-DNA transformation. Somatic genetic variations (SGV) in DNA from MFD-1, tumour, normal oesophagus, and leucocytes were analysed genome wide with the SNP6 DNA microarray (Affymetrix). WGS was performed in tumour and leucocyte DNA. Functional studies of MFD-1 were performed *in vitro* (3D culture + immunohistochemistry (IHC)) and *in vivo* (SCID mouse xenograft).

Results: MFD-1 showed >97% concordance with matched tumour on genome wide SNP6 analysis confirming derivation from the source malignancy. MFD-1 and the source tumour shared identical SGV in established cancer promoting genes in EAC including deletions of SMAD4 and p16, and mutations in TP53 and the newly recognised DOCK2. In 3D culture MFD-1 was invasive and proliferative. Using IHC, MFD-1 stained strongly for pan-Cytokeratin and moderately for CK 7, confirming its glandular epithelial phenotype. MFD-1 formed tumours in SCID mice that developed more rapidly than the historical EAC cell lines OE33 and Flo-1.

Conclusions: The clinical utility of whole genome sequencing projects will be the development of molecular-phenotype therapeutics. To achieve this model, systems that faithfully represent the tumour of origin are required. We have described the first such system (MFD-1) to arise from the oesophageal ICGC project. Authentication of MFD-1 confirms that it is a representative invasive tumour model and contains somatic deletions/mutations in the most commonly mutated genes in EAC (p16, SMAD4 & TP53) and the invasion-promoting DOCK2.