PWE-020 USING MICROARRAY DATA TO ELUCIDATE THE MOLECULAR PHENOTYPE OF A NOVEL ONCOGENE AND IDENTIFY A THERAPEUTIC STRATEGY

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¹C-A J Ong, ²N B Shannon,* ²O M Rueda, ³R Hardwick, ²C Caldas, ¹R C Fitzgerald. ¹MRC Cancer Cell Unit, Cambridge, UK; ²Cambridge Research Institute, Cambridge, UK; ³Cambridge Oesophago-gastric Centre, Cambridge, UK

Introduction The incidence of esophageal and junctional adenocarcinoma has increased sixfold in the past 30 years. Despite aggressive chemotherapy and attempts at curative surgery, the 5-year survival rate remains at 20%. Unlike other epithelial cancers, targeted therapy is limited. We have identified TRIM44 as a putative oncogene that is amplified in 8% of EA and 6% of breast cancers.

Methods The aims of this project were to elucidate the molecular phenotype underlying the oncogenic role of TRIM44 as well as suggest ways to therapeutically target TRIM44 dysregulation.

Results Using three microarray datasets representing EA (n=37, n=64) and breast (n=997) we performed gene set enrichment analysis to identify signalling pathways dysregulated with TRIM44 high expression (EA and breast) or amplification (breast only). High expression of TRIM44 was associated with over-enrichment of targets of the mTOR pathway consistent across all three data sets. This association was validated using expression microarrays in a cell line (HSC39) with amplification of TRIM44 treated with siRNA. Using phosphorylation of p70S6K as a readout of mTOR activity we validated the link between TRIM44 and the mTOR pathway; knockdown of TRIM44 using siRNA in HSC39 and a cell line with high expression of TRIM44 (JIMT-1) resulted in a decrease in pathway activity. The connectivity map (<http://www.broad-institute.org/cmap/>), a collection of expression array data derived from lines treated with bioactive small molecules was queried using signatures generated from the microarray data representing genes positively or negatively associated with TRIM44 (breast, EA, HSC39 +SiRNA datasets). The top consistent hits were sirolimus, an mTOR inhibitor and analogue of rapamycin and LY-294002, a PI3K inhibitor. These hits represent small molecules predicted to reverse the effects of high TRIM44 expression. Treatment with inhibitors in HSC39 and JIMT-1 demonstrated that these lines were highly sensitive (IC₅₀<30 nM) to rapamycin, but less sensitive to PI3K inhibition (IC₅₀>400 nM), consistent with a link at the level of mTOR.

Conclusion We have demonstrated the ability to identify a previously unknown association between TRIM44 and the mTOR pathway using expression and copy number data. This phenotype was validated in cell line experiments and highlighted a potential therapeutic strategy using analogues of rapamycin, a small molecule inhibitor of the mTOR pathway, which are currently in clinical use as immunosuppressants and in clinical trials for other cancer types.

Competing interests None declared.

PWE-021 SECONDARY CARE COSTS IN OESOPHAGOGASTRIC CANCER IN THE UK: A SINGLE CENTRE MICRO-COSTING STUDY

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¹N Stern,* ²A Bassi, ^{1,3}K Bodger. ¹Department of Gastroenterology, Aintree University Hospital NHS Foundation Trust, Liverpool, UK; ²Department of Gastroenterology, St Helens and Knowsley Hospitals NHS Trust, Prescot, UK; ³Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Introduction Published data describing the scale, profile and determinants of healthcare resource use for oesophago-gastric cancer

(OGC) are scarce, particularly for the UK. The National Cancer Plan (2000) encouraged greater use of imaging for staging and increased use of oncological therapies but the major modalities of palliation and curative surgery have changed little over the last decade. We have reported how emergency presentation predicts a poor outcome¹ and now aimed to study the effect of this mode of presentation on resource use and cost.

Methods Using cohorts of all patients presenting with OGC to a single university hospital trust (Aintree University Hospital, Liverpool, UK) over two, 2-year periods (July 1997–June 1999 and Jan 2001–Dec 2002) we audited all resource use from referral to diagnosis and 12 months post-diagnosis or death (whichever was sooner). Diagnostic and staging investigations, in-patient bed days and treatments including surgical, oncological and endoscopic were all itemised. Patient treatment was categorised according to initial intent. Individual hospital based unit costs or HRG tariffs (2010/2011 financial year) were applied to derive per-patient costs for the cohorts.

Results Of 333 patients identified, 320 had complete data to enable cost analysis. Median cost per-patient was £11965.94 with annualised costs to our institution of £1.2 million. Potentially curative treatment accounted for 32.5% of institutional costs, palliation 56.2% and supportive care 11.3%. Per-patient costs [median (IQR)]: Curative treatment: £11863.80 (9701–17430); Palliative treatments: £14288.52 (10016–22710); Supportive care only: £6619.96 (3567–11778). Emergency presentations (31.2% of cases) consumed 30.8% of cost despite shorter survival with significant increased costs per live day (£148.14 vs 71.61, p<0.001), mostly due to longer inpatient stays. Linear regression of log transformed costs confirms that emergency presentation increased cost per live day independently of age or potentially curative treatment. Endoscopic interventions were used in 33.4% patients.

Conclusion Managing OGC has a significant impact on healthcare resources with most expenditure is for those treated with palliative intent. Presenting as an emergency increases costs per live-day compared to elective presentation. These primary data can support modelling studies of cost-effectiveness of rival programmes or treatments for OGC.

Competing interests None declared.

REFERENCE

1. **Shawihdi M**, Stern N, Thompson E, *et al*. Emergency admission as a route for oesophago-gastric cancer diagnosis: a marker of poor outcome and a candidate quality indicator for local services. *Gut* 2011;**60**(Suppl 1):A30–1.

PWE-022 COMPLETION RATES OF PALLIATIVE CHEMOTHERAPY ARE LOW IN PATIENTS WITH OESOPHAGO-GASTRIC CANCER: RESULTS FROM A NATIONAL AUDIT

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¹O Groene,* ²R Hardwick, ³S Riley, ⁴T Crosby, ⁵K Greenaway, ⁶D Cromwell. ¹Health Services Research and Policy, London School of Hygiene & Tropical Medicine, London, UK; ²Addenbrooke's, Cambridge, UK; ³Northern General Hospital, Sheffield, UK; ⁴Velindre Cancer Center, Cardiff, UK; ⁵NHS Information Centre, Leeds, UK; ⁶London School of Hygiene & Tropical Medicine, London, UK

Introduction Palliative chemotherapy is routinely offered to patients diagnosed with locally advanced or metastatic oesophago-gastric cancer. Based on data from the National Oesophago-Gastric Cancer Audit (NOGCA), we describe the characteristics of patients being offered palliative chemotherapy, determine the proportion of patients completing treatment, and identify factors associated with treatment completion.

Methods The NOGCA prospectively collected data on patients diagnosed with invasive epithelial cancer of the oesophagus or

stomach between 1 October 2007 and 30 June 2009. For patients receiving palliative oncology, we compared characteristics of completers and non-completers of chemotherapy using χ^2 tests and multiple logistic regression models with correction for cluster sampling. For variables with missing data we imputed values using multiple imputation by chained equations.

Results Of 16 264 patients participating in the NOGCA in England, 2313 received palliative chemotherapy treatment. Female patients or patients of older age were less likely to receive treatment. Overall, only 39.7% completed their treatment. Factors associated with treatment completion were low performance status, high age and high level of deprivation. In our study, treatment completion was not related with site of cancer, pre-treatment stage, sex, co-morbidities or histology.

Conclusion Completion rates of palliative chemotherapy in patients with oesophago-gastric cancer are low. The low completion rates may reflect the complex medical decision making for this group of patients and the need to balance survival benefits, toxicity of treatment, patients' preferences and patients' quality of life. Patients unlikely to complete chemotherapy may be more appropriately managed on a palliative supportive care pathway with symptom control.

Competing interests None declared.

REFERENCES

1. **Cromwell DA**, Palser T, Van der Meulen J, et al. The National Oesophageal-Gastric Cancer Audit: Third Annual Report. London: The Information Centre, 2010.
2. **Lord SR**, Hall PS, McShane P, et al. Factors predicting outcome for advanced gastroesophageal cancer in elderly patients receiving palliative chemotherapy. *Clin Oncol (R Coll Radiol)* 2010;**22**:107–13.
3. **Koedoot CG**, de Haan RJ, Stiggelbout AM, et al. Palliative chemotherapy or best supportive care? A prospective study explaining patients' treatment preference and choice. *Br J Cancer* 2003;**89**:2219–26.
4. **Braga S**. Why do our patients get chemotherapy until the end of life? *Ann Oncol* 2011;**22**:2345–8.

PWE-023 PROGNOSTIC SIGNIFICANCE OF CIRCUMFERENTIAL RESECTION MARGIN STATUS IN OESOPHAGEAL CANCER—A SYSTEMATIC REVIEW AND META-ANALYSIS

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¹O Rotimi, ²D Greenwood, ²Y-K Tu. ¹Department of Histopathology, Leeds Teaching Hospitals Trust, Leeds, UK; ²Biostatistics Unit, Centre for Epidemiology & Biostatistics, University of Leeds, Leeds, UK

Introduction The status of the circumferential resection margin (CRM) in oesophageal cancer has been suggested as a prognostic factor but the reports are conflicting. Also, there are two methods of defining positive CRM—within 1 mm (Royal College of Pathologists, RCPATH UK)¹ and 0 mm (College of American Pathologists, CAP).²

Methods A systematic review was carried out using a pre-defined protocol and papers that met the inclusion criteria were selected. Data extracted from those with required adjusted HR for meta-analysis using STATA-11 statistical software. Assessments were made for heterogeneity, publication bias, small study effects and sensitivity analysis for influence.

Results Fourteen cohort studies^{3–16} were systematically reviewed but nine^{4, 5, 9, 10–15} meta-analysed. Abstract PWE-023 table 1 shows the results of the pooled overall and CRM criteria sub-group estimates. There was significant heterogeneity between the studies (p value<0.001 and I² value of 74.8%). There was evidence of publication bias and small study effects (Egger's test p value 0.029). None of the studies had undue influence.

Abstract PWE-023 Table 1 Results of fixed effects meta-analysis by CRM criteria

Method	HR (95% CI)	Test of effect	Test of heterogeneity	I ² value
RCPATH criteria (UK)	1.45 (1.27 to 1.66)	<0.0001	0.003	72.70%
CAPcriteria (USA)	2.61 (1.90 to 3.59)	<0.0001	0.33	9.90%
Overall	1.58 (1.40 to 1.79)	<0.0001	<0.001	74.80%

Conclusion This meta-analysis provides evidence that the CRM status in oesophageal carcinoma has prognostic significance. This significance is present irrespective of the criteria used for defining the margin but the estimate for the 0 mm CAP criterion is much higher than those of the within 1 mm RCPATH criterion. The overall HR of 1.58 (95% CI 1.40 to 1.79) suggests patients with positive CRM have 60% more risk of death compared to patients with a negative margin. The significant heterogeneity and publication bias are limitations to the study and the former in particular requires further analysis.

Competing interests None declared.

REFERENCES

1. *The RCPATH Dataset for the Histopathological Reporting of Oesophageal Carcinoma*. 2007.
2. *An Overview of the College of American Pathologists Cancer Checklists*. 2009.
3. **Chao Y-K**, et al. *Ann Surg Oncol* 2011;**18**:529.
4. **Deeter M**, et al. *Arch Surg* 2009;**144**:618.
5. **Dexter SP**, et al. *Gut* 2001;**48**:667.
6. **Khan OA**, et al. *BJC* 2003;**88**:1549.
7. **Sagar PM**, et al. *BJS* 1993;**80**:1386.
8. **Saha AK**, et al. *Ann Surg Oncol* 2009;**16**:1364.
9. **Scheepers JJ**, et al. *Dis Esophagus* 2009;**22**:42.
10. **Sujendran V**, et al. *BJS* 2008;**95**:191.
11. **Verhage RJJ**, et al. *Am J Surg Pathol* 2011;**35**:919.
12. **Griffiths EA**, et al. *EJSO* 2006;**32**:413.
13. **Pultrum BB**, et al. *Ann Surg Oncol* 2010;**17**:812.
14. **Mirnezami R**, et al. *Int J Surg* 2010;**8**:58.
15. **Thompson S**, et al. *Ann Surg Oncol* 2008;**15**:3447.
16. **Roh MS**, et al. *Korean J Pathology* 2004;**38**:23.

PWE-024 PREVALENCE, MANAGEMENT AND OUTCOME OF SUBMUCOSALLY INVASIVE CANCERS IN A WESTERN OESOPHAGOGASTRIC EMR POPULATION

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P J Basford,* R J Mead, M D Duku, G R Longcroft-Wheaton, P Bhandari. *Department of Gastroenterology, Portsmouth Hospitals NHS Trust, Portsmouth, UK*

Introduction Risk of lymph node metastases depends on good or bad prognostic features of submucosally (SM) invasive cancer specimen following endoscopic resection (ER). Invasion limited to SM1 level, lack of lymphovascular invasion and well differentiated grade are good prognostic features and may indicate that radical resection is not required following ER. However, depth of SM invasion can be very difficult to assess in ER specimens and hence a "safe" strategy would be to offer radical surgery to all patients with SM invasive disease, irrespective of other features. This is the policy we follow. We aimed to evaluate the outcome of these cancers in an ER population.

Methods All Upper Gastrointestinal ER procedures for the period 2005–2011 were recorded on a prospective database. All procedures were carried out by a single skilled endoscopist. Demographic data, histology, procedure success, long-term outcome and complications were assessed. Careful endoscopic assessment using chromoendoscopy, plus CT/EUS where appropriate, were performed prior to attempted endoscopic resection and afterwards if indicated.

Results Cancer with submucosal invasion was detected in 26 of 123 (21.1%) cases of oesophagogastric neoplasia. 22 patients were male and the mean age was 75.2 years (range 54–84 years). Submucosal invasion was present in 16 of 74 (21.6%) lesions arising in Barrett's