Association of tumour vascularisation and glucose metabolism with neoadjuvant therapy response in primary oesophageal and gastro-oesophageal cancer

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Background

- Oesophageal cancer is increasing in incidence

- Despite best multimodality therapy overall prognosis remain poor[1]
    - 50% relapse within 2 years of surgery
    - 47% 5yr survival rate

- Highlights need for better pre-operative prognostication than current TNM staging to improve selection for therapy

- Hypothesis: tumour vascular and/or metabolic phenotype can predict response to neoadjuvant therapy

1. van Hagen P et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. New England Journal of Medicine. 2012;366(22):2074-84

Aims

- To assess whether imaging biomarkers of tumour vascularisation and/or metabolism (assessed with DCE-MRI and 18F-FDG PET/CT, respectively) can predict response to neoadjuvant therapy by pathology criteria

DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging
18F-FDG PET/CT: 18F-fluorodeoxyglucose positron emission tomography

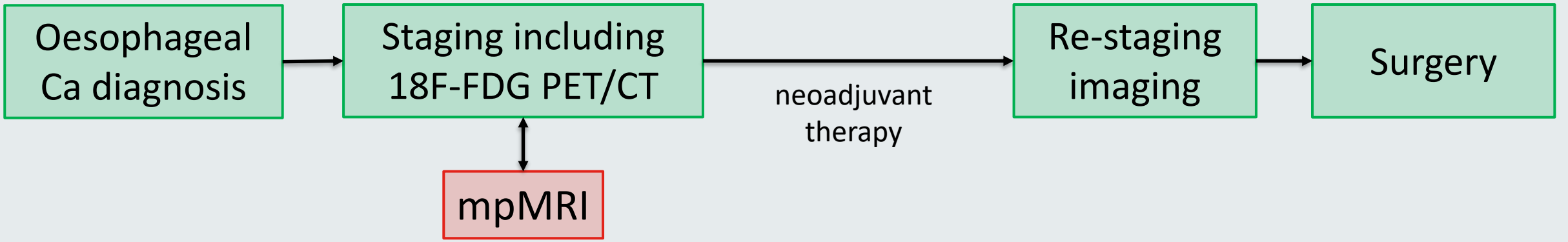
Methods

- Ethical approval gained (REC13/LO/0027)

- Inclusion criteria:
  - Adult patients
  - Histologically-proven oesophageal or oesophagogastric cancer
  - Stage II-III (T2-4 N0-3 M0)
  - ECOG performance status 0-2
  - Candidates for curative treatment (surgery +/- neoadjuvant therapy or definitive chemoradiation)

- Exclusions: inability to consent; contraindication to DCE-MRI; previous resection of the tumour; previous radiotherapy to the thorax; chemotherapy within prior 3 months

Methods



DCE-MRI performed at time of PET/CT in patients meeting inclusion criteria

Multiparametric MRI protocol (Siemens 1.5T MAGNETOM Aera)

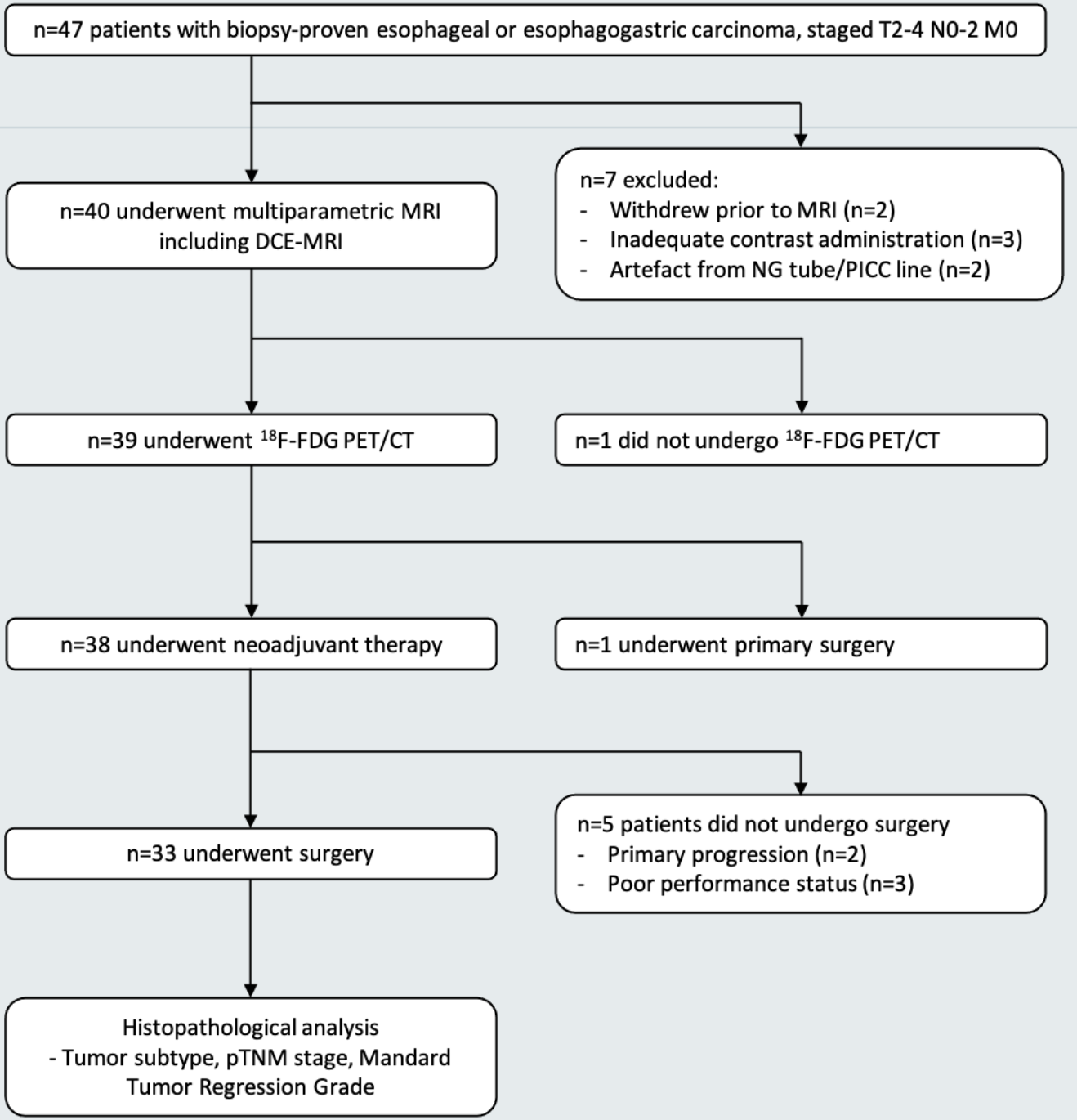
- 2D axial & coronal T2w HASTE
- DWI, b=0, 100, 900 s/mm^2
- 3D GE T1W fat-sat; pre- and dynamic post-contrast (temporal resolution 13s)

18F-FDG PET/CT (GE Discovery 750)

- 400MBq 18F-FDG IV & 60±5min uptake
- Vertex to mid-thigh
- CT acquisition 140 kVp, dose modulated mA, 3mm reconstructed slice thickness

Methods

Participant flowchart:



Methods

18F-FDG PET/CT analysis

- Hermes Hybrid Viewer; tumour volume of interest created using automated SUV thresholding
- **SUV_{max}**, **SUV_{mean}**, metabolic tumour volume (**MTV**); and total lesion glycolysis (**TLG** = SUV_{mean} x MTV)

DCE-MRI analysis

- Siemens Tissue 4D; following motion correction and registration, ROI drawn manually on 5 axial images at the centre of the tumour, combined to give average values
- Qualitative/Semi-quantitative:
  - **Curve type** (I – slow rising; II – plateau; III - washout)
  - **iAUC** (initial area under time-to-signal intensity curve): reflects both tumour perfusion and permeability
  - **PEI** (Positive enhancement integral): highest value of Gadolinium (Gd) concentration achieved prior to washout
- Quantitative (using Tofts pharmacokinetic modelling[1]):
  - **K^{trans}** (transfer constant, min^{-1}): rate of leakage of Gd from blood plasma into the extracellular extravascular space (EES)
  - **V_e** (Relative volume of EES, range 0-1): relative amount of interstitial space available to accumulate Gd
  - **K_{ep}** (rate constant, min^{-1}): rate of reflux of Gd from EES, back into the vasculature

1) Tofts PS, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. J Magn Reson Imaging. 1999;10(3):223-32.

Methods

Neoadjuvant therapy

- Patients received either:
  - Neoadjuvant chemoradiation, as per CROSS protocol[1]
  - Neoadjuvant chemotherapy (ECX or FLOT)

Histopathological assessment

- TNM stage; tumour subtype
- Mandard tumour regression grade (TRG)[2]
  - 1-3: responders
  - 4-5: non-responders

Statistical methods

- Multivariate logistic regression model created (single imaging biomarker combined with baseline clinical information (age, gender, T- stage, N-stage)); effect estimates calculated with odds ratio

1) Shapiro J, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
2) Noordman BJ, et al. Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study. Lancet Oncology. 2018;19(7):965-74

Results

Participant characteristics (for n=39 patients undergoing MRI and PET/CT)

	Number	Percentage
Gender		
Female	9	23%
Male	30	77%
Age		
<60 years	15	38%
≥60 years	24	62%
T stage		
T2	4	10%
T3	34	87%
T4	1	3%
N stage		
N0	8	21%
N1	16	41%
N2	13	33%
N3	2	5%

	Number	Percentage
Histology		
Adenocarcinoma	33	85%
Squamous cell carcinoma	6	15%
Tumour location		
Mid	2	5%
Low	17	44%
Esophagogastric	20	51%
Treatment		
Chemoradiation	3	8%
Chemotherapy	2	5%
Surgery alone	1	3%
Neoadjuvant chemoradiation + surgery	3	8%
Neoadjuvant chemotherapy + surgery	30	77%
Pathological response assessment *		
Mandard TRG 1-2	11	33%
Mandard TRG 3-5	22	67%

* Pathological response assessment in n=33 patients undergoing surgery following neoadjuvant therapy

Results

Multivariate analysis: Imaging variables in prediction of response assessment, adjusted for baseline clinical information (gender, age, T stage, N stage)

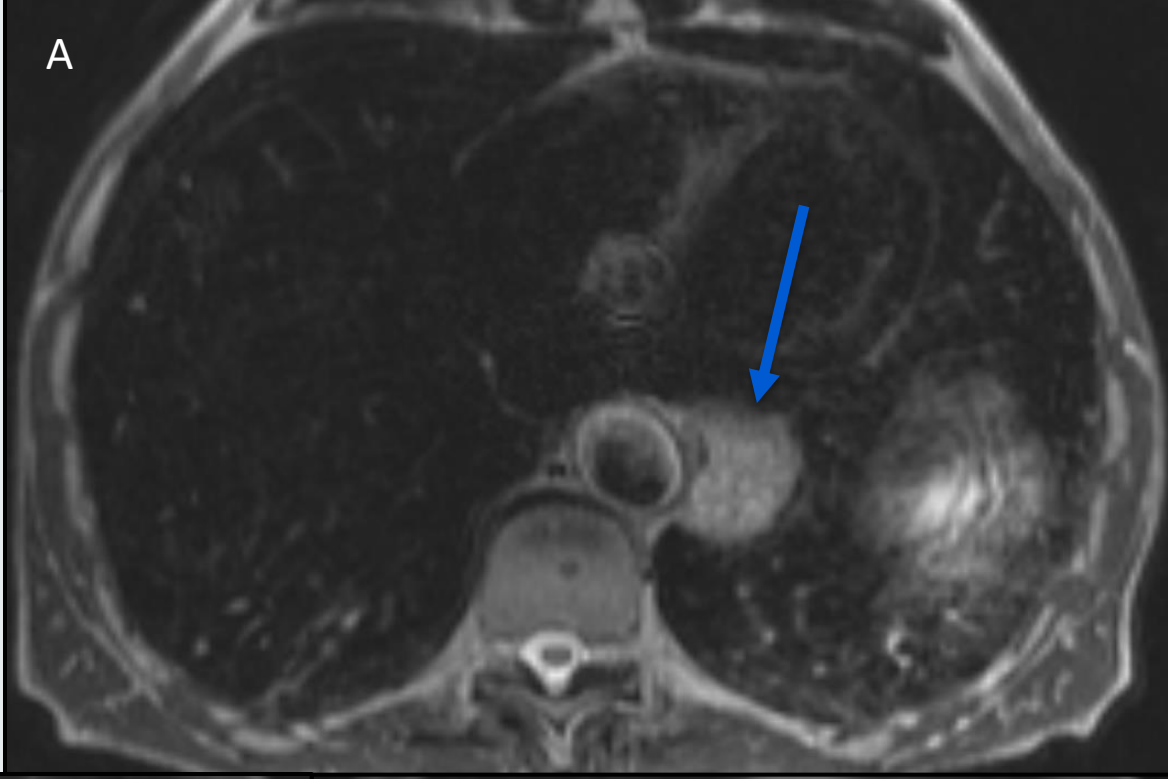
	Odds Ratio	95% Confidence interval	Area under ROC curve	p-value
MRI				
Semi-quantitative				
PEI *	0.95	0.90 - 1.00	0.87	0.03
iAUC *	1.03	0.99 - 1.07	0.80	0.14
Quantitative				
K^{trans} (min^{-1}) *	1.13	1.00 - 1.28	0.87	0.05
V_e *	1.01	0.97 - 1.06	0.75	0.66
K_{ep} (min^{-1}) *	1.02	0.99 - 1.05	0.78	0.30
18F-FDG PET				
SUV_{max}	1.02	0.89 - 1.18	0.76	0.75
SUV_{mean}	1.03	0.79 - 1.35	0.76	0.81
MTV (cm^3)	0.99	0.92 - 1.05	0.77	0.67
TLG	1.00	1.00 - 1.01	0.76	0.98

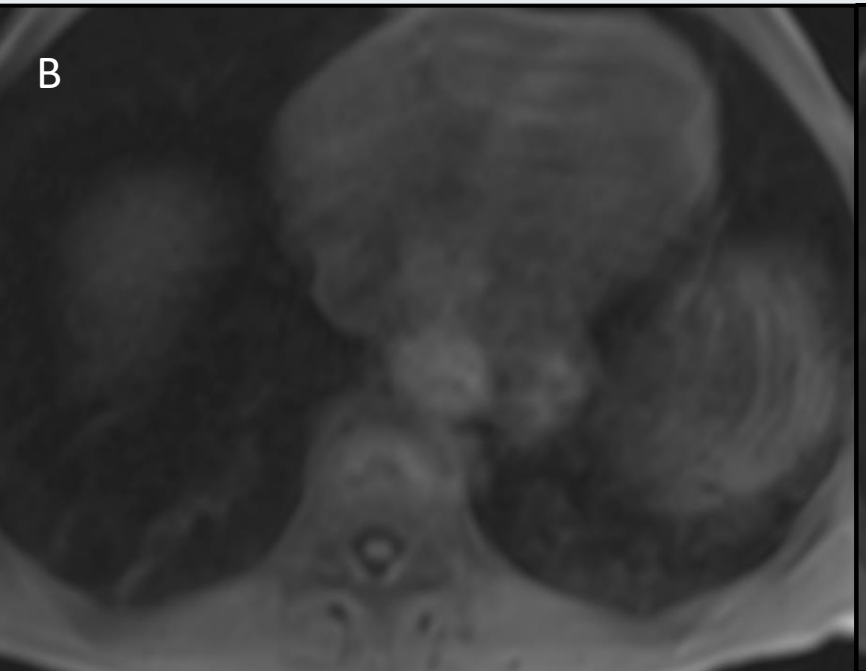
* MRI variables were multiplied by 100 prior to statistical analysis due to the small numerical values.

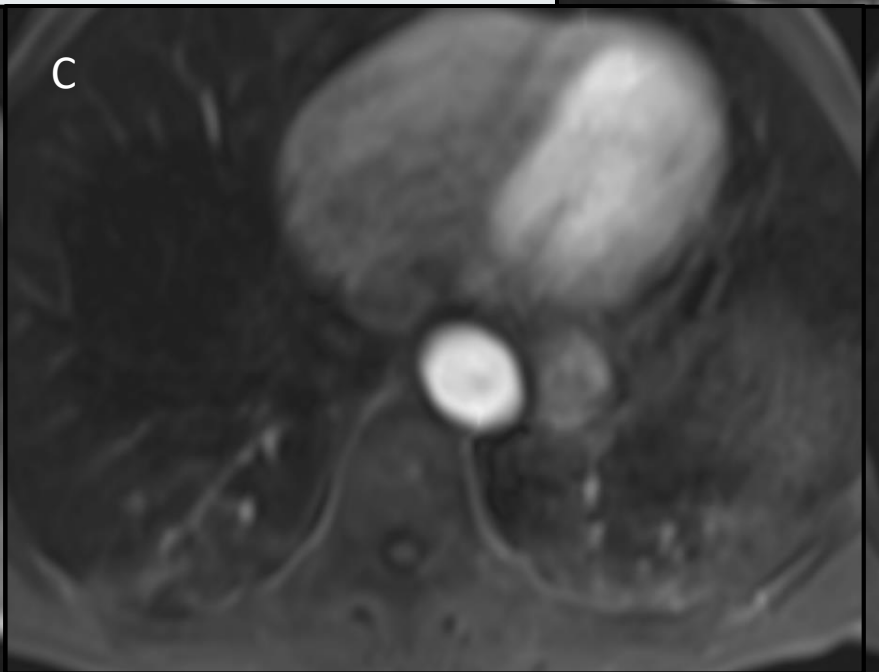
Results

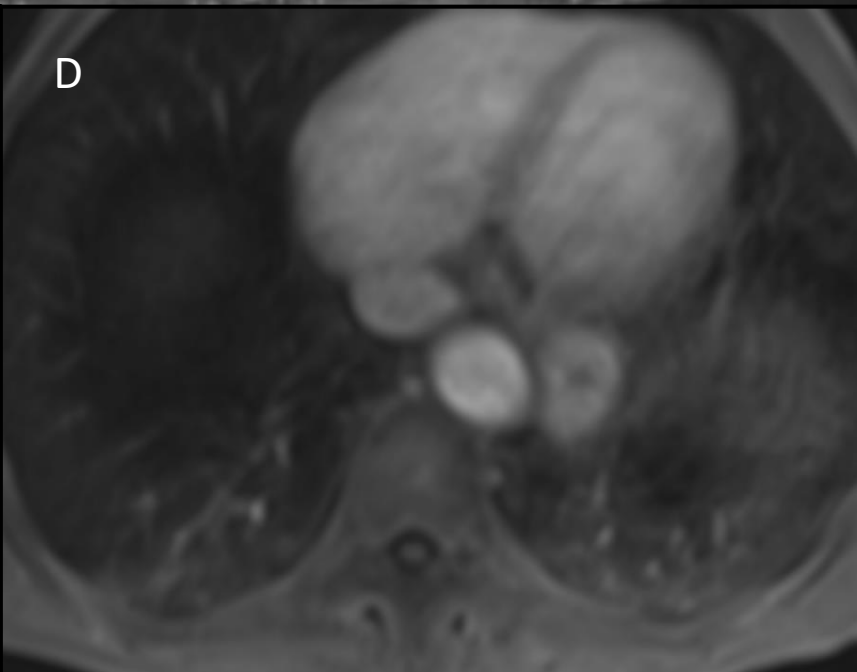
78-year-old male with oesophageal adenocarcinoma, clinically staged at T3 N1 M0. Poor response to neoadjuvant therapy (Mandard TRG 5); tumour in 4/35 resected lymph nodes.

Axial T2-weighted image (A) demonstrating the lower oesophageal adenocarcinoma; unenhanced (B), post-contrast arterial (C) and portal venous phase (D) T1-weighted images showing early enhancement followed by washout in the lesion.

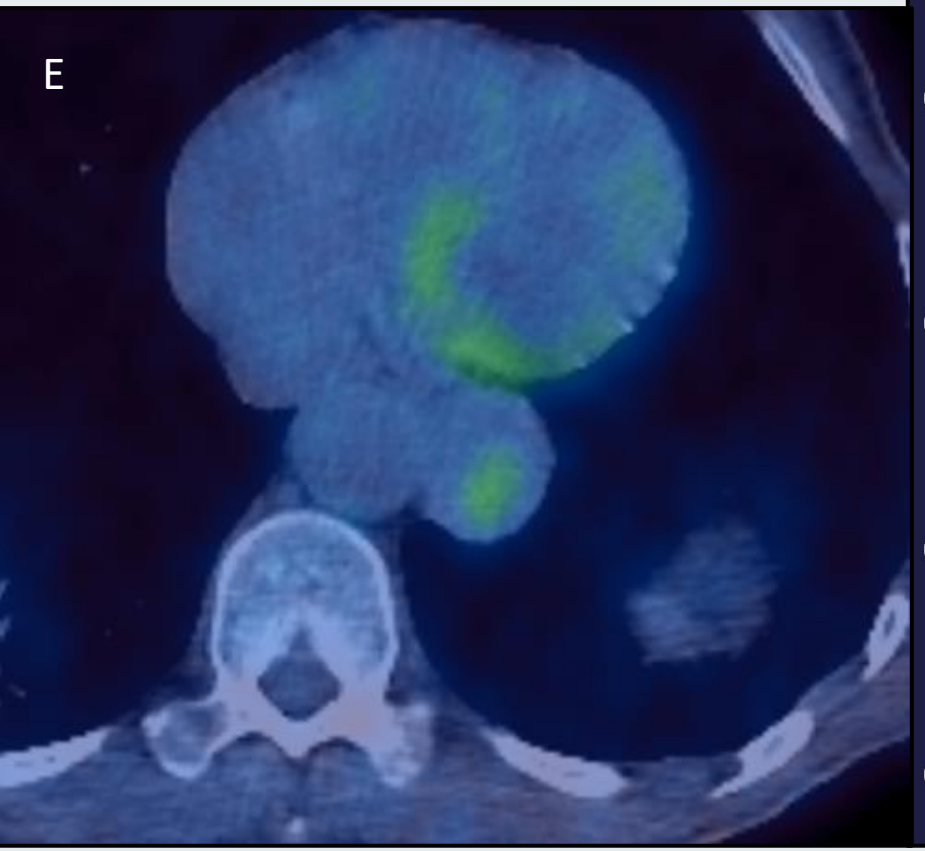


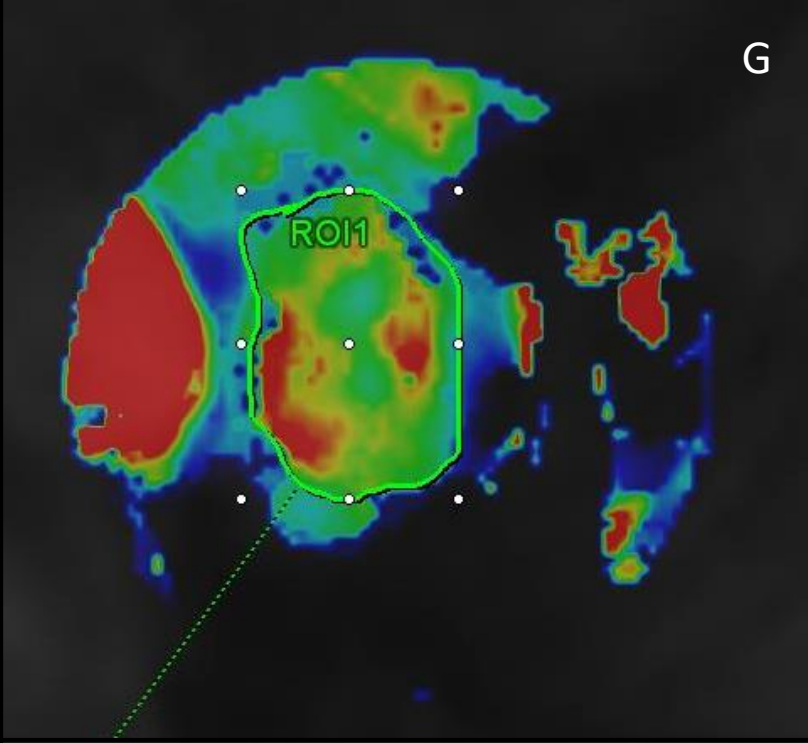


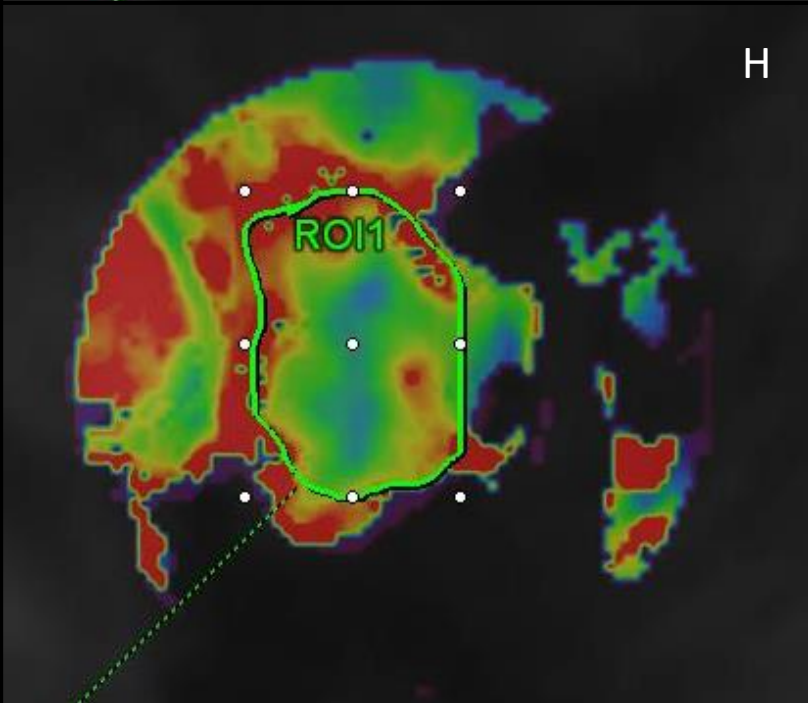




Results







18F-FDG PET/CT image (E) showing low tumor metabolic activity with SUV_{max} of 4.1 and total lesion glycolysis of 21. Time-gadolinium concentration curve with washout (F). K^{trans} map (G) and peak enhancement integral (PEI) map (H) with tumor regions-of-interest shown (K^{trans}: 0.40 s^{-1}; PEI: 0.22).

Results

Key results

In multivariate analysis (single imaging variable, corrected for age, gender, T stage and N stage):

- PEI predictive of response: **odds of response decreased by 5% for each 0.010 increase in PEI** (OR – 0.95; 95% CI 0.90-1.00; p=0.03)
- K^{trans} predictive of response: **odds of response increased by 13% for each 0.010 increase in K^{trans}** (OR – 1.13; 95% CI 1.00 – 1.28; p=0.05)
- PET parameters not predictive of response

Discussion

Hypothesis for findings & clinical relevance

- Higher PEI was associated with decreased likelihood of response
  - PEI may reflect increased neo-angiogenesis/biological aggression
- Higher K^{trans} was associated with increased likelihood of response
  - K^{trans} may reflect greater perfusion/delivery of chemotherapy agents[1]

- Imaging biomarkers that can predict response to neoadjuvant can help lead to individualised care:
  - Non-responders (TRG 3-5) typically comprise 75% of patients undergoing neoadjuvant therapy[2]
  - Patients unlikely to respond to standard neoadjuvant therapy could be considered for intensification of treatment or proceed directly to surgery
  - Patients likely to undergo complete pathological response (TRG 1) could be considered for omission of surgery/organ-sparing treatment

1) Ye ZM, et al. DCE-MRI-Derived Volume Transfer Constant (K(trans)) and DWI Apparent Diffusion Coefficient as Predictive Markers of Short- and Long-Term Efficacy of Chemoradiotherapy in Patients With Esophageal Cancer. Technol Cancer Res Treat. 2018;17:1533034618765254.
2) Noble F, et al. Multicentre cohort study to define and validate pathological assessment of response to neoadjuvant therapy in oesophagogastric adenocarcinoma. Br J Surg. 2017;104(13):1816-28.

Conclusion

- DCE-MRI biomarkers for tumour neoangiogenesis & perfusion appear predictive of response to neoadjuvant therapy in primary oesophageal/oesophagogastric carcinoma.

Questions

- For any questions, please email – samuel.withey@nhs.net

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