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Radiological prediction of positive circumferential resection margin in oesophageal cancer

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ABSTRACT

Purpose: A positive circumferential resection margin (CRM) is regarded as a poor prognostic indicator in oesophageal cancer (OC) but its prediction can be challenging. MRI is used to predict a threatened CRM in rectal cancer but is not commonly performed in OC unlike PET/CT, which is now routinely used. Therefore, this study assessed the additional predictive value of PET-defined tumour variables compared with EUS and CT T-stage. The prognostic significance of CRM status was also assessed.

Materials and Methods: This retrospective study included 117 consecutive patients [median age 64.0 (range 24–78), 102 males, 110 adenocarcinomas, 6 squamous cell carcinoma (SCC), 1 neuro-endocrine] treated between 1st March 2012 and 31st July 2015. A binary logistic regression model tested 5 staging variables; EUS T-stage (≤T2 vs ≥ T3), CT T-stage (≤T2 vs ≥ T3), PET metabolic tumour length (MTL), PET metabolic tumour width (MTW) and the maximum standardised uptake value (SUV_{max}).

Results: The CRM was positive in 43.6%. Sixty-seven (57.3%) patients received neo-adjuvant chemotherapy (NACT), 31 patients (26.5%) underwent surgery alone and 19 patients (16.2%) had neo-adjuvant chemoradiotherapy (NACRT). Median overall survival (OS) was 36.0 months (95% confidence interval (CI) 24.1–47.9) and the 2-year OS was 55.4%. A binary logistic regression model showed EUS ≥ T3 tumours were independently and significantly more likely to have a positive CRM than EUS ≤ T2 tumours (HR 5.188, 95% CI 1.265–21.273, p = 0.022). CT T-stage, PET MTL, PET MTW and SUV_{max} were not significantly associated with CRM status (p = 0.783, 0.852, 0.605 and 0.413, respectively). There was a significant difference in OS between CRM positive and negative groups (X^2 4.920, df 1, p = 0.027).

Conclusion: Advanced EUS T-stage is associated with a positive CRM, but PET-defined tumour variables are unlikely to provide additional predictive information. This study demonstrates the continued benefit of EUS as part of a multi-modality OC staging pathway.

1. Introduction

The impact of circumferential resection margin (CRM) involvement on patient outcome in oesophageal cancer (OC) has been widely reported [1–3]. Although some studies have failed to demonstrate the prognostic significance of an involved or threatened CRM [4,5], it is now widely accepted that a positive resection margin is important [6]. Analysis from the USA Intergroup 113 trial investigated the effect of CRM status on survival [7]. Thirty-two percent of patients with a R0 resection were alive and disease-free at 5 years, compared to only 5% survival in those with a R1 resection.

Prediction of pathological CRM involvement could influence treatment selection, potentially improving overall survival (OS) and recurrence rates. Clinicians may have a lower threshold for offering neo-adjuvant therapy to patients at risk. In general, fit patients with tumours of stage T3/T4a, N0/N1, or T1/T2 N1, are considered for neo-adjuvant therapy. Following publication of MRC OE02, the current standard treatment in the UK is neo-adjuvant chemotherapy (NACT) followed by surgery, although neo-adjuvant chemoradiotherapy (NACRT) is gaining support and may eventually become standard of care [8–10].

In the UK, patients with OC are initially staged with contrast-

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enhanced computed tomography (CT) to exclude unresectable disease or distant metastases. Patients with potentially curable disease then routinely undergo EUS and positron emission tomography (PET) combined with CT (PET/CT) for more detailed staging [11]. PET/CT is predominately used to exclude distant metastases not demonstrated on CT, and for treatment planning. Image features including metabolic tumour length (MTL), metabolic tumour width (MTW) and the maximum standardised uptake value (SUV_{max}) are prognostic indicators of survival and treatment response [12,13].

There is currently limited evidence investigating the association between PET-defined tumour variables and a threatened CRM. MRI accurately predicts a positive CRM in rectal cancer [14], however early MRI studies in OC encountered initial difficulties because the examination is technically challenging [15]. Alternative methods are required to improve CRM prediction in OC. PET-defined tumour variables may provide additional predictive value when assessing the CRM.

Therefore, this study investigated the additional value of PET-defined tumour variables (MTL, MTW and SUV_{max}) compared with EUS and CT T-stage, to predict a threatened CRM. The prognostic significance of a positive CRM was also assessed.

2. Methods and materials

2.1. Patient cohort

A retrospective cohort study was conducted in consecutive patients with biopsy-proven OC treated between 1st March 2012 and 31st July 2015. Patients with gastro-oesophageal junction (GOJ) tumours were included. Clinical, radiological, surgical and pathological data were reviewed from a prospectively maintained surgical upper gastro-intestinal (GI) cancer database in a University teaching hospital.

Patients were identified for inclusion at the centralised Regional Upper GI Cancer MDT and deemed to have potentially curable disease following clinical examination, upper GI endoscopy and radiological staging investigations. All patients underwent PET/CT examination in the same institution using the same scanner and protocol and had surgical resection (with or without neo-adjuvant therapy) in the centralised regional service. Institutional review board granted approval for the study (13//DMD5769). Patients were excluded from the study if the patient had incomplete staging, salvage oesophagectomy after radical radiotherapy or an 'open-and-close' procedure (aborted resection). Following exclusions, 117 patients were included in the study.

2.2. Radiological staging

Radiological staging was classified according to International Union Against Cancer (UICC) Tumour Node Metastasis (TNM) 7th edition [16]. PET/CT examinations were reported by Consultant Radiologists with minimum of 5 years' experience. EUS was performed in 3 centres by 4 experienced endosonographers.

2.3. CT protocol

CT was performed either in the host institution of the centralised service, or in the local referring hospitals, according to Royal College of Radiologists guidelines [11]. All CT examinations were reviewed at the Regional Upper GI MDT, and deemed to be of a satisfactory technical standard. At the host institution, CT was performed with a GE HD 750 Discovery 64-slice scanner (GE Healthcare, Pollards Wood, Buckinghamshire, UK). CT images were acquired by a helical acquisition with collimation of 40 mm, pitch 0.984:1 and tube rotation speed of 0.4 s. Tube output was 120 kVp with smart mA dose modulation between 60–600 mA. Slice thickness was 0.625 mm with acquisition of images on soft and lung algorithms with 3 mm reconstructions. Approximately 500 ml of water was given orally. Between 100–150 ml of Niopam 300 was given intravenously.

2.4. EUS technique

At the host institution, an initial endoscopic examination was performed using a 9 mm diameter Olympus Paediatric gastroscope (Olympus, Southend, UK) to assess the degree of oesophageal luminal stenosis. Patients with an estimated oesophageal luminal diameter of less than 15 mm underwent examination using the smaller-diameter MH-908 oesophagoprobe, and where there was no luminal stenosis, the standard UM-2000 echoendoscope was used (Olympus, Southend, UK). The type of echoendoscope used was at the discretion of the endoscopist. No significant difference in accuracy exists between the 2 echoendoscopes [17]. The primary oesophageal tumour was assessed, together with an evaluation of the para-oesophageal anatomical structures as described previously [18].

2.5. PET/CT protocol

Patients were fasted for at least 6 h prior to tracer administration. Serum glucose levels were routinely checked and confirmed to be less than 7.0 mmol/L. Patients received a dose of 4 MBq of ^{18}F-FDG per kilogram of body weight. Uptake time was 90 min. ^{18}F-FDG PET/CT imaging was performed with a GE 690 PET/CT scanner (GE Healthcare, Buckinghamshire, UK). CT images were acquired in a helical acquisition with a pitch of 0.98 and a tube rotation speed of 0.5 s. Tube output was 120 kVp with output modulation between 20 and 200 mA. Matrix size for the CT acquisition was 512 × 512 pixels with a 50 cm field of view. No oral or intravenous contrast was administered. PET images were acquired at 3 min per field of view. The length of the axial field of view was 15.7 cm. Images were reconstructed with the ordered subset expectation maximisation algorithm, with 24 subsets and 2 iterations. Matrix size was 256 × 256 pixels, using the VUE Point ™ time of flight algorithm (Fig. 1).

2.6. PET-defined tumour variables

PET MTL is defined as the maximum perceived cranio-caudal length of primary tumour and was measured on a GE advantage windows 4.5 reporting workstation (GE healthcare, Buckinghamshire, UK) by a single observer with 5-years' experience of PET research. The observer was blinded to the histopathological results and used consistent methodology. The maximum intensity projection images were rotated to visualise the greatest length of tumour and MTL was measured in mm. MTW is defined as the maximum perceived width of primary tumour perpendicular to the MTL and was measured in mm. The SUV_{max} of the

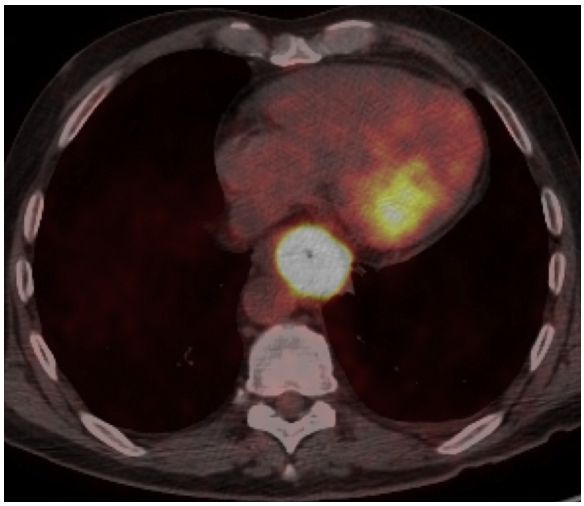

Fig. 1. Axial fused PET/CT image of a distal oesophageal adenocarcinoma which had a positive CRM following surgical resection.