Acute radiation oesophagitis associated with FDG uptake on PET/CT during chemo-radiation therapy in patients with non-small cell lung cancer.

Sarah Everitt	PhD[1,2,3]
Jason Callahan	BAppSci, Med Rad (NM)[3,4]
Eman Obeid	BAppSci, Med Rad (RT)[1]
Rodney J Hicks	MD FRACP2[2,4]
Michael Mac Manus	MD FRCR FRANZCR[1,2]
David Ball	MD FRANZCR[1,2]

1 Division of Radiation Oncology, Peter MacCallum Cancer Centre, Locked Bag 1 A'Beckett Street, Victoria, 8006, Australia

2 Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, 3010, Australia

3 Department of Medical Imaging & Radiation Sciences, Faculty of Medicine, Nursing & Health Sciences, Monash University, Clayton, Victoria, Australia

4 Centre for Cancer Imaging, Peter MacCallum Cancer Centre, Locked Bag 1 A'Beckett Street, Victoria, 8006, Australia

Address correspondence to: Dr Sarah Everitt, Radiation Therapy Services, Peter MacCallum Cancer Centre, Locked Bag 1 A'Beckett Street, Victoria, 8006, Australia

Phone 61 3 8559 6025 Fax 61 3 8559 7379 Email: sarah.everitt@petermac.org

Running title : Radiation oesophagitis detected on FDG PET/CT

DR. SARAH EVERITT (Orcid ID : 0000-0001-6785-0067)
DR. DAVID BALL (Orcid ID : 0000-0002-0491-6919)

Article type : Radiation Oncology Original Article

Abstract

Introduction: Acute radiation oesophagitis (ARO) is frequently experienced by patients receiving concurrent chemo-radiation therapy (cCRT) for non-small cell lung cancer (NSCLC). We investigated ARO symptoms (CTCAE v3.0), radiation dose and oesophageal FDG PET/CT uptake.

Method: Candidates received cCRT (60Gy, 2Gy/fx) and sequential FDG PET/CT (baseline FDG_0, FDG_{wk2} and FDG_{wk4}). Mean and maximum standardized uptake value (SUVmean and SUVmax) and radiation dose (Omean and Omax) were calculated within the whole oesophagus and seven sub-regions (5 - 60 Gy).

Results: 44 patients underwent FDG_0 and FDG_{wk2}, and 41 (93%) received FDG_{wk4}, resulting in 129 PET/CT scans for analysis. Of 29 (66%) patients with ≥ grade 2 ARO, SUVmax (mean ± SD) increased from FDG_0 to FDG_{wk4} (3.06 ± 0.69 to 3.83 ± 1.27, ρ = 0.0019) and FDG_{wk2} to FDG_{wk4} (3.10 ± 0.75 to 3.83 ± 1.27, ρ = 0.0046). Radiation dose (mean ± SD) was higher in grade ≥2 patients; Omean (47.5±20 vs 53.9±10.2, p=0.0061), Omax (13.7±9.6 vs 20.1±10.6, p=0.0009) and V40Gy (8.0±8.2 vs 11.9±7.3, p=0.0185).

Conclusions: FDG_{wk4} SUVmax and radiation dose were associated with ≥ grade 2 ARO. Compared to subjective assessments, future interim FDG PET/CT acquired for disease response assessment may also be utilised to objectively characterise ARO severity and image-guided oesophageal dose constraints.

Introduction

Acute oesophagitis is frequently experienced by patients receiving curative intent radiation therapy (RT) for non-small cell lung cancer (NSCLC), especially when administered concurrently with chemotherapy (cCRT) (1, 2). Oesophagitis can cause severe odynophagia which necessitates feeding interventions, hospitalization and treatment breaks, which may negatively impact overall survival (3).

Numerous radiation dose metrics, including maximum and mean dose (Gy), have been reported in the literature to be associated with the probability of clinically significant ARO (4-8). However, unlike other thoracic organs, oesophagus-sparing plans and population-based dose constraints are not routinely employed in clinical practice, nor do they necessarily reflect the radio-sensitivity of an individual patient. ARO is subjectively graded according to the patient's symptoms and so, unlike most other toxicity scales, lacks objectivity.

2-deoxy-2-[18F]fluoro-D-glucose- (FDG) is the established positron emission tomography (PET) radiotracer in NSCLC when combined with computed tomography (CT) for tumour diagnosis, staging and RT target delineation (9, 10). Despite its high sensitivity for tumour imaging, the specificity of FDG-PET decreases in the presence of non-neoplastic inflammation or stromal cells, which also demonstrate increased expression of glucose transporters (11, 12) and have been associated with radiation pneumonitis on post-cCRT FDG-PET (13, 14). This negative attribute for tumour imaging may present a powerful approach for monitoring radiation induced inflammatory changes during treatment.
Our team conducted a prospective study investigating NSCLC response to cCRT using FDG PET/CT scans acquired during week two and week four of therapy. The acquisition of these scans enabled us to undertake this sub-study investigating FDG oesophageal uptake in NSCLC patients during cCRT. Hence, the primary aim of this prospective study was to investigate FDG oesophageal uptake on sequential PET/CT scans taken during cCRT. We also examined the relationship between oesophageal FDG uptake, radiation dose volumetrics and the clinical severity of ARO and neutropenia.

Material and methods

Sixty patients were recruited into a prospective IRB approved single arm study of sequential PET/CT imaging during cCRT for NSCLC at the Peter MacCallum Cancer Centre (Australian Clinical Trials Registry ACTRN12611001283965). Data of all patients were eligible for inclusion in this sub-study. All patients provided written informed consent. Patient eligibility included stage I-IIIB histologically confirmed NSCLC, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, weight loss of less than 10%; and were planned to receive radical cCRT. Radiation was prescribed to 60Gy in 30 fractions, 5 per week on a Varian CLINAC 21iX or Varian Trilogy (Varian Medical Systems, Palo Alto, CA, USA) with 6MV photons. Chemotherapy was either cisplatin (50 mg/m2) on days 1 and 8 (cycle 1) and 29 and 36 (cycle 2) and etoposide (50 mg/m2 daily during weeks 1 and 5), or weekly carboplatin (area under the curve, 2) and paclitaxel (45 mg/m^2). Patients were excluded if they had received previous thoracic RT.

Three-dimensional FDG PET/CT studies were acquired at baseline (FDG_0), week 2 (FDG_{wk2}) and week 4 (FDG_{wk4}) of cCRT [PET/CT STE (GE Healthcare) or Biograph (Siemens Medical Solutions)]. Each patient fasted for at least six hours prior to an intravenous injection of FDG (4.2 MBq/kg, 0.114mCi). Baseline emission scans were initiated 60 min after injection, and all subsequent scans were scheduled according to the baseline uptake time. Patients were positioned in the supine RT treatment position with laser localisation for every scan (16).

3D conformal RT (3DCRT) dosimetry was calculated on Xio (Computerized Medical Systems CMS, St Louis, MO, USA) using a fast superposition algorithm. Dosimetry, based on FDG_0 PET/CT defined target volumes, was calculated for 60 Gy. The exact radiation dose delivered immediately prior to FDG_{wk2} and FDG_{wk4} PET/CT was calculated for every patient on the respective scans. Following dose calculations, PET and CT, radiation dose data and tumour volumes were exported to MIM (version 6.3.2, MIM Software Inc., Cleveland, OH, USA) for contouring and analysis. The outer muscular oesophageal perimeter was delineated from the cricoid to the gastro-oesophageal junction on CT, using pre-defined soft-tissue window/level settings (15). Anatomical and dosimetric endpoints included the maximum (Omax) and mean (Omean) oesophageal doses and percentage volume of oesophagus receiving 5 Gy and 10 to 60 Gy (Vx, in 10 Gy increments). Isodose lines were converted to structures to facilitate a quantitative analysis of tracer uptake within pre-specified radiation dose regions. The volume and intensity of tracer uptake (maximum and mean standardised uptake values, SUV_{max} and SUV_{mean}) was recorded for the total oesophageal volume and within radiation dose regions of 5Gy, 10Gy, 20Gy and 30Gy at baseline, week two and week four.

The presence and grade of ARO and neutropenia were assessed in accordance with Common Toxicity Criteria for Adverse Events (CTCAE v3.0) (16). The oesophagitis grading scale is shown in Figure 1. Acute toxicities were defined from the first day of treatment to day 90. During cCRT, prospective oesophagitis assessments were conducted by the treating radiation oncologist at weekly intervals. Following treatment completion, all available oesophagitis assessment data were collected retrospectively from electronic medical records. These records were reported by the patient's radiation oncologist or a lung unit nurse. A complete blood count was performed prior to every chemotherapy administration and all neutropenia data were collected retrospectively from the patient's electronic medical record.

Statistical analyses were performed with GraphPad Prism 6 (version 6.04, GraphPad Software, La Jolla, CA, USA). For all analyses, patients were dichotomized according to the maximum ARO grade experienced (Grade 0-1 vs Grade 2-3). Differences in oesophageal dose between toxicity groups and FDG uptake at each time-point between toxicity groups were calculated using the non-parametric Mann-Whitney test. Differences in FDG uptake (SUVmax and SUVmean) were calculated between time-points using Wilcoxon matched-pairs signed rank test and across three time-points using one-way ANOVA. The association between ARO and neutropenia was examined with Fisher's exact test. All ρ values were two-tailed and values <0.05 were considered statistically significant.

Results

Data of 44 (73%) patients registered in the prospective FDG PET/CT tumour monitoring study between March 2009 – August 2013 were eligible for inclusion in this sub-study. Reasons for patient exclusion include treatment intent changed to palliative following FDG_0 (3 patients) and radiation dose data was unable to be exported from the Xio planning computer to MIM for analysis in 13 (22%) patients).

Of the 44 eligible patients, 34 (77%) were male and the median (range) age was 67 years (47 – 86 years). Patient demographic and tumour characteristics are presented in Table 1. No patient experienced a treatment break.

129 PET/CT scans available and eligible for review included 44 (100%) FDG_0 scans, 44 (100%) FDG_{wk2} and 41 (93%) $FDG_{wk4.}$ Patient exclusions at week 4 include one patient who withdrew from the trial in week three and two patients who ceased treatment at 26Gy and 20 Gy, respectively. The mean (SD) radiation dose at FDG_{wk2} was 14.5 Gy (± 2.3 Gy) and at FDG_{wk4} was 35.4 Gy (± 2.4 Gy).

Using the CTCAE v3.0 grading scale (Figure 1), at week two, 41 (93%) patients reported that they were experiencing grade 0-1 ARO and three (7%) patients reported grade 2 ARO. At week four, 30 (73%) patients reported grade 0-1 ARO, nine (22%) reported grade 2 ARO and two (5%) reported grade 3 ARO. In all patients the maximum ARO grade was experienced in the final week of cCRT, with grade 0-1 in 15 (34%) patients, grade 2 in 22 (50%) patients and grade 3 in seven (16%) patients. Of these 28 patients dichotomised to the maximum G2-3 group, at week four, five patients reported G0, 12 patients reported G1, nine patients reported G2 and two patients reported G3.

The median (range) patient weight at FDG_0 was 77 kg (48-124 kg), which changed by 0 kg (-4 to 5 kg) at FDG_{wk2} and +1kg (-5 to 7 kg) at FDG_{wk4}. Neutropenia data was available for 40 patients; 15 (38%) experienced grade ≥ 2 neutropenia including six (15%) grade 2, four (10%) grade 3 and five (13%) grade 4. Of these 15 patients, 12 (80%) experienced ≥ grade 2 ARO. Of the remaining 25 patients, 15 (38%) experienced no neutropenia with grade ≥ 2 ARO and 10 (25%) experienced no clinically significant ARO or neutropenia (OR = 2.667 95% CI [0.5966 to 11.92], ρ =0.2984).

For all patients, the total planned mean (±SD) Omax and Omean were 54.7 Gy (±15 Gy) and 20.6 (±11.34 Gy), respectively. At FDG_{wk2}, the mean (±SD) Omax and Omean were 13.5 Gy (±4.2 Gy) and 5.1 Gy (±2.8 Gy), respectively. At FDG_{wk4}, the mean (±SD) Omax and Omean were 34.3 Gy (±8.1 Gy) and 14.8 (±7.4 Gy), respectively. When dichotomised to those experiencing a maximum ARO grading of grade 0-1 vs grade 2-3, the Omax and Omean were significantly higher in patients reporting grade 2-3 ARO at all time-points (Table 2).

For the overall cohort, the mean (±SD) SUVmax for patients reporting a maximum ARO grade of 0, 1, 2 and 3 were 3.15 (±0.56), 3.16 (±0.85), 3.65 (±1.19) and 4.38 (±1.26). The difference in FDG uptake (SUVmax) between patients reporting Grade 0 ARO to those with Grade 3 ARO was statistically significant (p=0.05). Comparisons between other toxicity groups did not reach statistical significance (results not shown). Within the combined G2-3 toxicity group, the mean (±SD) SUVmax within the whole oesophagus assessed at each time-point was unchanged from FDG_0 to FDG_{wk2} (3.06 ± 0.69 to 3.10 ± 0.75, ρ=0.739), but significantly increased from FDG_0 to FDG_{wk4} (3.06 ± 0.69 to 3.83 ± 1.27, ρ = 0.0019) and FDG_{wk2} to FDG_{wk4} (3.10 ± 0.75 to 3.83 ± 1.27, ρ = 0.0046), as shown in Figure 2. The change across all three time-points was also statistically significant (ρ = 0.0037). No significant differences were observed within the G0-1 toxicity group when comparing the mean (±SD) SUVmax of 3.10 (±0.72), 3.22 (±0.77) and 3.16 (±0.83) on FDG_0, FDG_{wk2} and FDG_{wk4}, respectively (ρ = 0.8461). Figure 3 illustrates week two and week four FDG PET/CT scans of a patient with significantly increased oesophageal FDG uptake on $FDG_{wk4.}$

When analysing oesophageal sub-regions over time, significantly higher FDG uptake (SUVmax) was observed within 5Gy, 10Gy, 20Gy and 30Gy isodose regions in patients experiencing Grade 2-3 toxicities compared to those with Grade 0-1. As shown in Table 3, statistically significant differences in SUVmax within sub-regions were observed over time in the Grade 2-3 toxicity group, including 5 Gy (p=0.0023), 10 Gy (p=0.0028), 20Gy (p=0.0340) and 30 Gy (p=0.0239). Uptake within isodose sub-volumes on the baseline scans were calculated according to the projected absorbed dose for 60 Gy. The consistency between these values suggests no pre-treatment differences or pre-existing inflammatory pathologies between the toxicity groups.

At week two, three (7%) patients reported Grade 2 ARO. When analysed further, the maximum oesophageal dose received by these patients in week two was 18.8 Gy, 20.3 Gy and 16.5 Gy, which was considerably higher than the mean dose received by the overall G2-3 cohort at week two of 14.8 Gy. Further, the corresponding SUVmax within the 10 Gy isodose region of these patients was 3.11, 3.89 and 3.09, which was also considerably higher than the mean SUVmax of the overall G2-3 patient cohort at this time-point of 2.7.

SUVmean comparisons demonstrated no differences between toxicity groups. On FDG_0, the SUVmean within the unirradiated oesophagus was 1.48 and 1.44 (ρ = 0.3605) for grade 0-1 vs grade 2-3 ARO groups, respectively. Similarly, no significant differences were observed in SUVmean between groups on FDG_{wk2} (ρ=0.6199) or FDG_{wk4} (ρ=0.9581).

Discussion

Results of this prospective study provide an insight into the biological response of the oesophagus to cCRT according to the uptake of FDG on sequential PET/CT scans. Compared to asymptomatic patients, patients reporting clinically significant ARO (≥ grade 2) demonstrated significantly higher FDG uptake within the irradiated oesophagus on FDG_{wk4}. This suggests that FDG PET/CT can non-invasively and objectively monitor the location and severity of treatment induced inflammatory changes during cCRT.

We quantitatively analysed FDG uptake on PET/CT as a surrogate for ARO using the whole oesophageal volume and precise sub-volumes. At week two, only three (7%) patients reported Grade 2 ARO. These patients received higher radiation doses and had correspondingly higher FDG uptake (SUVmax) than the remaining patients in the G2-3 toxicity group. For all other patients no significant increases in FDG_{wk2} parameters were apparent at this early time-point. This was not unexpected since ARO is known to occur with increasing radiation exposure, leading to rapid mucosal epithelium (EPI) depletion, limited basal cell proliferation for epithelial repopulation and tissue inflammation approximately three weeks after the commencement of cCRT (17, 18). In contrast, a recent study of 27 cCRT patients by Mehmood et.al. reported 8 (30%) patients with grade 2 ARO at week two, significantly higher than our group receiving the same 2 Gy/day and platinum based chemotherapy (19). No difference was observed between G0 vs ≥ 1 patients in SUVpeak on FDG_{wk2} (ρ = 0.46), however

FDG_{wk2} SUVpeak was higher in patients who later developed grade 3 ARO ($\rho = 0.01$).

Our FDG_{wk4} data indicate significant increases in all SUVmax parameters in patients experiencing clinically significant ARO. Further, the severity of oesophagitis experienced by these patients peaked during or after the final week of cCRT. The presence of increased FDG uptake prior to patients reporting the maximum ARO severity could be useful in the supportive care of these patients in the future. These data are consistent with Yuan et.al. (2014) who used FDG oesophageal uptake at the axial level of the tumour as a surrogate for absorbed dose for 50 patients, demonstrating the mean ± SD normalised SUV increased significantly from FDG_0 (1.09 ± 0.05) to approximately 45 Gy of RT (1.28 ± 0.06), $\rho = 0.001$ (20). Mehmood et.al. (2016) dichotomised patients to ARO G0 vs ≥ 1, reporting significant increases in SUVpeak on FDG_{wk4} in 20 (74%) patients with G≥1 ARO ($\rho = 0.01$) (19). Nijkamp and colleagues (2013) investigated FDG oesophageal uptake in 82 patients using pre- and post-therapy PET/CT (21). Patients received 24 treatments of 2.75Gy per fraction and ≥ Grade 2 oesophagitis was reported in 57 (70%) patients. On post-therapy PET/CT the oesophageal FDG uptake ($SUV_{50\%}$) was significantly higher in patients with ≥ Grade 2 oesophagitis (2.2 vs. 2.6, $\rho < 0.01$). Overall, these observations of increased FDG uptake may suggest radiation injury to the oesophageal mucosa and an inflammatory state, or radiation induced metabolic damage, both producing increased glucose consumption.

The overall incidence and severity of ARO experienced by patients in our study, 22 (50%) grade 2 and seven (16%) grade 3, is similar to reports from other authors (5, 19). By the completion of cCRT, Mehmood et.al. (2016) reported 14 (52%) and 6 (22%) patients with grade 2 and 3 ARO, respectively (19). In a meta-analysis of 1082 patients, (median prescribed radiation dose of 65 Gy), Palma et.al (2013) reported ARO of grade 2 or more in 543 (49.9%) patients and concluded the volume of oesophagus receiving 60 Gy (V60) was the best predictor of G2 and G3 ARO (5). Mehmood et.al. (2016) reported no difference in Omax between patients with G0 vs G≥1 ARO, whereas we observed a significant difference in Omax between G0-1 and G2-3 severity groups (p=0.0061). Our data reporting associations between radiation dose and ARO are consistent with previous studies by our own team and others;

Omax, Omean and the volume of oesophagus receiving ≥ 35Gy were associated with clinically significant ARO (1, 5, 7, 22).

Although a greater proportion of patients with neutropenia grade ≥ 2 developed grade ≥ 2 oesophagitis (80%) than patients who did not experience neutropenia (38%), this was not statistically significant. However, it is not consistent with our previous study of oesophagitis and neutropenia, and work by De Ruysscher et.al (2007), where an association between these toxicities was observed (22, 23). The lack of a statistically significant association in the current study is likely due to the small sample size of 40 patients. Further research to explore this relationship is warranted in the future.

The presence of non-malignant oesophageal pathologies (e.g. candidiasis and oesophageal reflux), can result in false-positive uptake of FDG within the oesophagus. These factors were not studied in this cohort, however the absence of any differences between the baseline FDG uptake of the G0-1 vs G2-3 toxicity groups suggests these factors were not significant. Additionally, the pattern of FDG-uptake for these pathologies is very different. Whereas radiation oesophagitis is confined to the geographical extent of radiation damage, other aetiologies are more localised, e.g. lower oesophagus for reflux, or more diffuse, e.g. infective (candidiasis).

Dose volume metrics are population based and may inadequately predict the severity of ARO experienced by individual patients. A weakness of our study is that changes in SUV were correlated with ARO symptom grade, rather than an objective assessment of ARO such as severity of mucosal reaction observed at oesophagoscopy. Patients were only reviewed using the CTCAE ‘esophagitis’ grading scale, which is subjective, based on patient reporting of eating and swallowing symptoms and does not reflect symptoms such as pain. The inclusion of the CTCAE ‘esophageal pain’ grading scale into our routine clinical assessments in the future may provide additional information to measure the severity of ARO in these patients to ensure they receive optimal supportive care. An additional limitation of our study was our inability to capture toxicity data immediately following treatment completion, when the severity of ARO may have peaked. At our Centre, clinical follow-up is managed according to individual patient needs and it was beyond the scope of our study to assess patients once they had returned home.

As described, the opportunity to conduct this sub-study arose from the acquisition of serial scans performed for a separate tumour monitoring study at our centre. In the context of this study, the latest scan (FDG_{wk4}) was most likely acquired prior to the development of the most severe oesophagitis (early following treatment completion). Although the acquisition of additional FDG PET/CT scans during, or following, treatment is unlikely to be initiated for toxicity assessments alone, if performed for tumour monitoring purposes these scans would enable real-time, individualized inflammatory assessments for future patients (23, 24). Spatially accurate information regarding the location and intensity of FDG uptake on week four scans provides quantitative and objective information that could assist clinicians considering intensified therapies with adaptive volumes to minimize additional oesophageal irradiation. All of this may become more relevant if adaptive radiotherapy based on changes in tumor FDG uptake during treatment, currently under investigation by several groups (e.g. http://www.kccop.org/pdfs/FullProtocol-1361163321.pdf), is found to be of value and becomes a standard of care. One further potential clinical diagnostic application of identifying FDG inflammatory uptake within the irradiated volume is to exclude other causes of chest pain or odynophagia (e.g. cardiac pain or oesophageal cancer).

Conclusions

In addition to established radiation dosimetrics, an association was observed between ≥ grade 2 ARO and FDG uptake on week four PET/CT during cCRT. In addition to their planned purpose of assessing tumour response, these findings suggest FDG_{wk4} is also an effective method of monitoring treatment induced oesophageal damage. Future applications of this work may include using interim scans to objectively measure ARO severity and to develop image-guided oesophageal dose constraints.

Acknowledgements

This work was supported by the National Health and Medical Research Council (APP1003895) and Victorian Cancer Agency (SJE). The authors thank Nicholas

Hardcastle for assistance with data transfer, study coordinator Jenny Trinh, radiation therapy and nuclear medicine colleagues for scanning patients and Mary Duffy, Laura Sparks, Alissa Michienzi, Nicole Kiss and Lineker Mai for assistance with data collection.

References

1. Belderbos J, Heemsbergen W, Hoogeman M, Pengel K, Rossi M, Lebesque J. Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy. Radiother Oncol. 2005;75(2):157-64.

2. Werner-Wasik M, Pequignot E, Leeper D, Hauck W, Curran W. Predictors of severe esophagitis include use of concurrent chemotherapy, but not the length of irradiated esophagus: a multivariate analysis of patients with lung cancer treated with nonoperative therapy. Int J Radiat Oncol Biol Phys. 2000;48(3):689-96.

3. Cox JD, Pajak TF, Asbell S, Russell AH, Pederson J, Byhardt RW, et al. Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials. Int J Radiat Oncol Biol Phys. 1993;27(3):493-8.

4. Ozgen A, Hayran M, Kahraman F. Mean esophageal radiation dose is predictive of the grade of acute esophagitis in lung cancer patients treated with concurrent radiotherapy and chemotherapy. J Radiat Res. 2012;53(6):916-22.

5. Palma DA, Senan S, Oberije C, Belderbos J, de Dios NR, Bradley JD, et al. Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: an individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2013;87(4):690-6.

6. Rodriguez N, Algara M, Foro P, Lacruz M, Reig A, Membrive I, et al. Predictors of acute esophagitis in lung cancer patients treated with concurrent three-dimensional conformal radiotherapy and chemotherapy. Int J Radiat Oncol Biol Phys. 2009;73(3):810-7.

7. Takeda K, Nemoto K, Saito H, Ogawa Y, Takai Y, Yamada S. Dosimetric correlations of acute esophagitis in lung cancer patients treated with radiotherapy. Int J Radiat Oncol Biol Phys. 2005;62(3):626-9.

8. Werner-Wasik M, Paulus R, Curran WJ, Jr., Byhardt R. Acute esophagitis and late lung toxicity in concurrent chemoradiotherapy trials in patients with locally advanced non-small-cell lung cancer: analysis of the radiation therapy oncology group (RTOG) database. Clin Lung Cancer. 2011;12(4):245-51.

9. Hicks RJ, MacManus M, Kalff V, Binns DS, Ware R, Hogg A, et al. Clinical Impact of PET Scanning in Patients Being Staged with Non-Small-Cell Lung Cancer (NSCLC) in a Radiation Oncology Facility. Clin Positron Imaging. 1999;2(6):329.

10. Konert T, Vogel W, MacManus MP, Nestle U, Belderbos J, Gregoire V, et al. PET/CT imaging for target volume delineation in curative intent radiotherapy of non-small cell lung cancer: IAEA consensus report 2014. Radiother Oncol. 2015;116(1):27-34.

11. Love C, Tomas MB, Tronco GG, Palestro CJ. FDG PET of infection and inflammation. Radiographics. 2005;25(5):1357-68.

12. Zhuang H, Yu JQ, Alavi A. Applications of fluorodeoxyglucose-PET imaging in the detection of infection and inflammation and other benign disorders. Radiol Clin North Am. 2005;43(1):121-34.

13. Mac Manus MP, Ding Z, Hogg A, Herschtal A, Binns D, Ball DL, et al. Association between pulmonary uptake of fluorodeoxyglucose detected by positron emission tomography scanning after radiation therapy for non-small-cell lung cancer and radiation pneumonitis. Int J Radiat Oncol Biol Phys. 2011;80(5):1365-71.

14. Abdulla S, Salavati A, Saboury B, Basu S, Torigian DA, Alavi A. Quantitative assessment of global lung inflammation following radiation therapy using FDG PET/CT: a pilot study. Eur J Nucl Med Mol Imaging. 2014;41(2):350-6.

15. Werner-Wasik M, Yorke E, Deasy J, Nam J, Marks LB. Radiation dose-volume effects in the esophagus. International journal of radiation oncology, biology, physics. 2010;76(3 Suppl):S86-93.

16. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003;13(3):176-81.

17. Murro D, Jakate S. Radiation esophagitis. Arch Pathol Lab Med. 2015;139(6):827-30.

18. Fountain MD, Abernathy LM, Lonardo F, Rothstein SE, Dominello MM, Yunker CK, et al. Radiation-Induced Esophagitis is Mitigated by Soy Isoflavones. Front Oncol. 2015;5:238.

19. Mehmood Q, Sun A, Becker N, Higgins J, Marshall A, Le LW, et al. Predicting Radiation Esophagitis Using (18)F-FDG PET During Chemoradiotherapy for Locally Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2016;11(2):213-21.

20. Yuan ST, Brown RK, Zhao L, ten Haken RK, Gross M, Cease KB, et al. Timing and intensity of changes in FDG uptake with symptomatic esophagitis during radiotherapy or chemo-radiotherapy. Radiat Oncol. 2014;9(1):37.

21. Nijkamp J, Rossi M, Lebesque J, Belderbos J, van den Heuvel M, Kwint M, et al. Relating acute esophagitis to radiotherapy dose using FDG-PET in concurrent chemo-radiotherapy for locally advanced non-small cell lung cancer. Radiother Oncol. 2013;106(1):118-23.

22. Everitt S, Duffy M, Bressel M, McInnes B, Russell C, Sevitt T, et al. Association of oesophageal radiation dose volume metrics, neutropenia and acute radiation oesophagitis in patients receiving chemoradiotherapy for non-small cell lung cancer. Radiat Oncol. 2016;11(1):20.

23. De Ruysscher D, Dehing C, Bremer RH, Bentzen SM, Koppe F, Pijls-Johannesma M, et al. Maximal neutropenia during chemotherapy and radiotherapy is significantly associated with the development of acute radiation-induced dysphagia in lung cancer patients. Ann Oncol. 2007;18(5):909-16.

24. Niedzielski JS, Yang J, Liao Z, Gomez DR, Stingo F, Mohan R, et al. (18)F-Fluorodeoxyglucose Positron Emission Tomography Can Quantify and Predict Esophageal Injury During Radiation Therapy. Int J Radiat Oncol Biol Phys. 2016;96(3):670-8.

Table 1: Patient and tumour characteristics (N=44)

Characteristic	N	%
Age (years)		
Median	67	
Range	47 – 86	
Sex		
Male	34	77
Histology		
Adenocarcinoma	19	43
Squamous cell carcinoma	16	36
Large cell carcinoma	3	7
Unclassified	6	14
Baseline Tumour Stage		
T Stage		
X	1	2
1	14	32
2	18	41
3	7	16
4	4	9
N Stage		
0	8	18
1	7	16
2	15	34
3	14	32
M Stage		
0	44	100

Table 2: Oesophagus dose volume data at week 2 and week 4 (actual dose delivered) and total prescribed dose (baseline plan, 60Gy). Patients are dichotomised by maximum ARO severity (Grade 0-1 vs Grade 2-3). Vx; volume of oesophagus receiving x Gy (%).

		ARO Grade 0–1 Mean ± SD	ARO Grade 2–3 Mean ± SD	ρ value
Omax (Gy)	Week 2	10.9 ± 5.2	14.8 ± 2.8	**0.0024**
	Week 4	31.0 ± 11.4	35.8 ± 5.5	0.0745
	60 Gy	47.5 ± 20	53.9 ± 10.2	**0.0061**
Omean (Gy)	Week 2	2.8 ± 1.7	6.3 ± 2.5	**<0.0001**
	Week 4	10.1 ± 7.0	17.0 ± 6.6	**0.0042**
	60 Gy	13.7 ± 9.6	20.1 ± 10.6	**0.0009**
V5 Gy (%)	Week 2	10.0 ± 9.5	18.8 ± 8.7	**0.0033**
	Week 4	20.5 ± 11.5	23.0 ± 9.4	0.4758
	60 Gy	21.9 ± 12.1	21.3 ± 8.6	0.6156
V10 Gy (%)	Week 2	5.3 ± 7.1	14.4 ± 9.0	**0.0014**
	Week 4	14.9 ± 10.9	21.2 ± 9.2	0.0601
	60 Gy	19.5 ± 11.8	19.4 ± 8.6	0.7275
V20 Gy (%)	Week 4	10.2 ± 9.1	17.1 ± 9.6	**0.0368**
	60Gy	12.3 ± 10.2	15.6 ± 7.9	0.0946
V30 Gy (%)	Week 4	6.6 ± 8.1	13.7 ± 9.0	**0.0202**
	60 Gy	10.3 ± 9.2	13.8 ± 7.7	0.0516
V40 Gy (%)	60Gy	8.0 ± 8.2	11.9 ± 7.3	**0.0185**
V50 Gy (%)	60Gy	7.5 ± 7.1	10.1 ± 6.4	0.0822
V60 Gy (%)	60Gy	2.5 ± 3.3	3.5 ± 4.4	0.3512

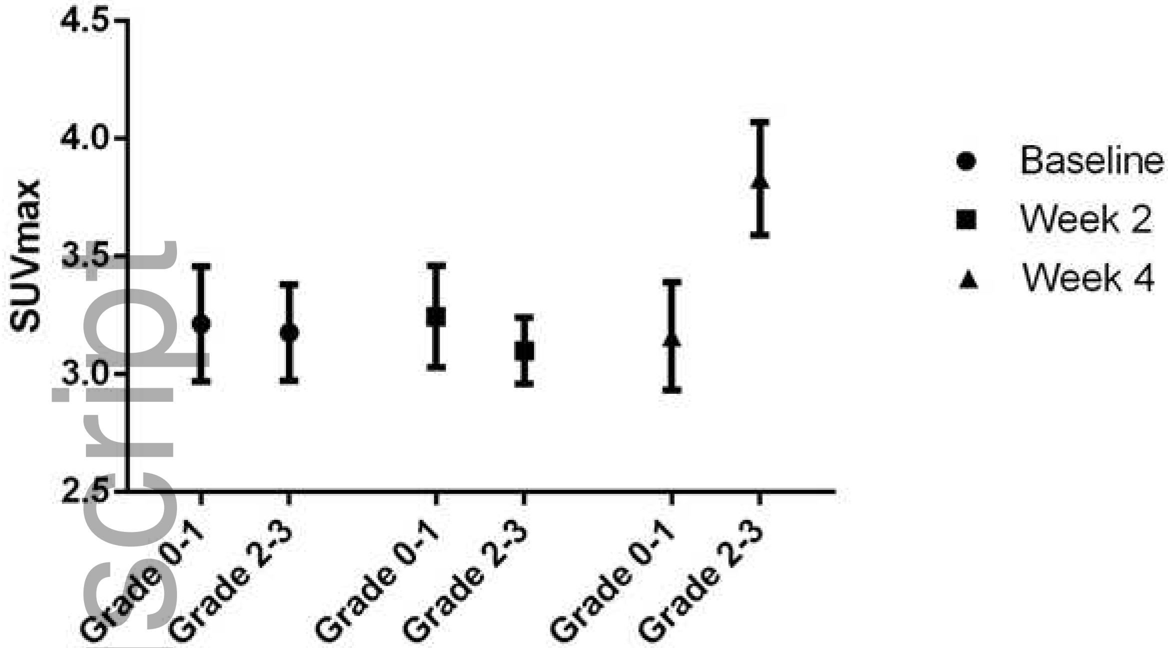
Table 3: FDG uptake (SUVmax) within predefined isodose regions according to toxicity group (Grade 0-1 versus Grade 2-3)

		Baseline Mean (±SD) SUVmax	Week 2 Mean (±SD) SUVmax	Week 4 Mean (±SD) SUVmax	p value
5 Gy	G0-1	2.62 ± 0.43	2.71 ± 0.58	2.86 ± 0.93	0.6712
	G2-3	2.91 ± 0.64	2.71 ± 0.54	3.54 ± 1.32	**0.0023**
10 Gy	G0-1	2.54 ± 0.51	2.53 ± 0.61	2.86 ± 0.98	0.4503
	G2-3	2.86 ± 0.66	2.66 ± 0.52	3.49 ± 1.33	**0.0028**
20 Gy	G0-1	2.59 ± 0.48	n.a.	2.81 ± 0.98	0.4935
	G2-3	2.86 ± 0.67	n.a.	3.50 ± 1.39	**0.0340**
30 Gy	G0-1	2.54 ± 0.48	n.a.	2.69 ± 1.05	0.6609
	G2-3	2.80 ± 0.59	n.a.	3.49 ± 1.43	**0.0239**

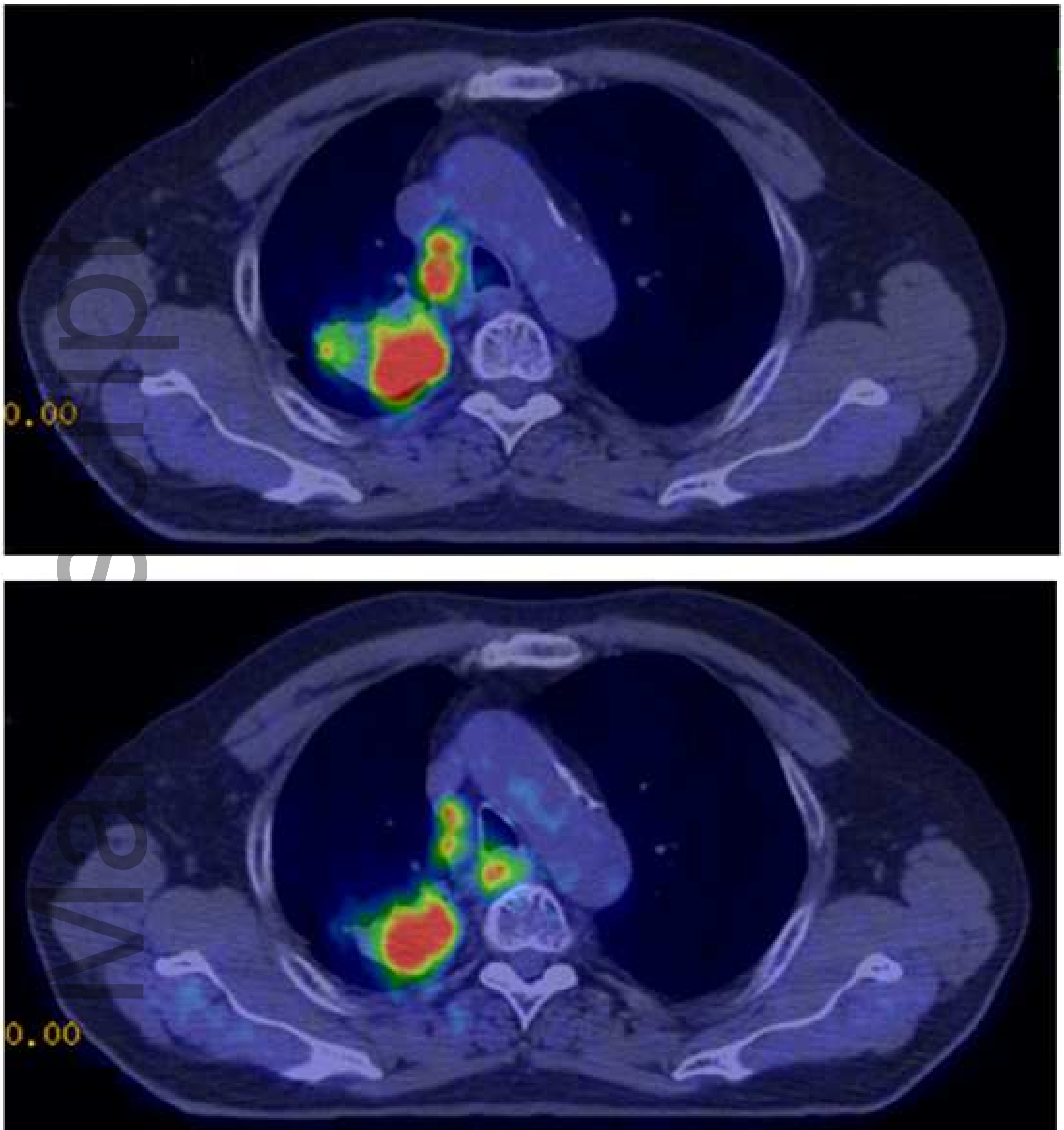
n.a. Not applicable as 20Gy and 30Gy were not delivered at the week two time-point. Baseline values were calculated on the baseline FDG PET/CT with planned isodose regions according to 60Gy prescribed dose.

0	1	2	3	4
None	Asymptomatic dysphagia; able to eat regular diet	Symptomatic; altered eating/swallowing (eg altered dietary habits, oral supplements)	Symptomatic & severely altered eating/swallowing (eg inadequate oral caloric or fluid intake); IV fluids, tube feeding	Life-threatening consequences; Obstruction, cannot swallow saliva, perforation

ara_12631_f1.jpg



ara_12631_f2.png



ara_12631_f3.png