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1 **External Validation of a Prognostic Model Incorporating Quantitative PET Image Features**  
2 **in Esophageal Cancer**

3  
4 KG Foley<sup>1</sup>, Z Shi<sup>2</sup>, P Whybra<sup>3</sup>, P Kalendralis<sup>2</sup>, R Larue<sup>2</sup>, M Berbee<sup>2</sup>, Sosef MN<sup>4</sup>, C Parkinson<sup>3</sup>, J  
5 Staffurth<sup>1,5</sup>, TDL Crosby<sup>5</sup>, SA Roberts<sup>6</sup>, A Dekker<sup>2</sup>, L Wee<sup>2</sup> and E Spezi<sup>3</sup>  
6

- 7 1. Division of Cancer & Genetics, School of Medicine, Cardiff University, UK  
8 2. Department of Radiation Oncology (MAASTRO Clinic), GROW – School for Oncology and  
9 Development Biology, Maastricht University Medical Centre, The Netherlands  
10 3. School of Engineering, Cardiff University, UK  
11 4. Zuyderland Medisch Centrum, Heerlen-Sittard-Geleen, The Netherlands  
12 5. Velindre Cancer Centre, Cardiff, UK  
13 6. Department of Clinical Radiology, University Hospital of Wales, Cardiff, UK  
14

15 **Corresponding Author**

16 Dr KG Foley

17 Division of Cancer & Genetics, School of Medicine, Cardiff University, CF14 4XN

18 Tel: +447795152790

19 Fax: +442920743029

20 E-mail: foleykg@cardiff.ac.uk  
21

1 **Abstract**

2

3 *Aim*

4 Enhanced prognostic models are required to improve risk stratification of patients with  
5 esophageal cancer so treatment decisions can be optimised. The primary aim was to  
6 externally validate a published prognostic model incorporating PET image features.  
7 Transferability of the model was compared using only clinical variables.

8

9 *Methods*

10 This was a Transparent Reporting of a multivariate prediction model for Individual Prognosis  
11 Or Diagnosis (TRIPOD) type 3 study. The model was validated against patients treated with  
12 neoadjuvant chemoradiotherapy according to the Neoadjuvant chemoradiotherapy plus  
13 surgery versus surgery alone for esophageal or junctional cancer (CROSS) trial regimen using  
14 pre- and post-harmonised image features. The Kaplan-Meier method with log-rank  
15 significance tests assessed risk strata discrimination. A Cox proportional hazards model  
16 assessed model calibration. Primary outcome was overall survival (OS).

17

18 *Results*

19 Between 2010 and 2015, 449 patients were included in the development (n=302), internal  
20 validation (n=101) and external validation (n=46) cohorts. No statistically significant  
21 difference in OS between patient quartiles was demonstrated in prognostic models  
22 incorporating PET image features ( $X^2=1.42$ ,  $df=3$ ,  $p=0.70$ ) or exclusively clinical variables (age,  
23 disease stage and treatment;  $X^2=1.19$ ,  $df=3$ ,  $p=0.75$ ). The calibration slope  $\beta$  of both models  
24 was not significantly different from unity ( $p=0.29$  and  $0.29$ , respectively). Risk groups defined  
25 using only clinical variables suggested differences in OS, although these were not statistically  
26 significant ( $X^2=0.71$ ,  $df=2$ ,  $p=0.70$ ).

27

28 *Conclusion*

29 The prognostic model did not enable significant discrimination between the validation risk  
30 groups, but a second model with exclusively clinical variables suggested some transferable  
31 prognostic ability. PET harmonisation did not significantly change the results of model  
32 validation.

33

34

35

36 **Keywords:** esophageal cancer; positron-emission tomography; radiomics; survival;  
37 prognosis

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1 **List of Abbreviations**

2

LNMs	lymph node metastases
PET	positron-emission tomography
NACRT	neo-adjuvant chemoradiotherapy
CROSS	Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer
TRIPOD	Transparent Reporting of a multivariate prediction model for Individual Prognosis Or Diagnosis
GI	gastrointestinal
MDT	multi-disciplinary team
CaNIS	Cancer Network Information System
ATLAAS	Automatic Tree-based Learning Algorithm for Advanced Segmentation
CI	confidence interval
TLG	tumour lesion glycolysis
OS	overall survival
IBSI	International Biomarker Standardisation Initiative

3

1 **Introduction**

2

3 The prognosis of patients with esophageal cancer is poor with overall 5-year survival  
4 approximately 15%. [1] Esophageal cancer is the eighth most common malignancy  
5 worldwide, accounting for around 400,000 deaths each year. [2]

6

7 Treatment strategies of patients with esophageal cancer are currently informed by  
8 radiological staging. Accurate staging is vital to inform clinicians of the likely prognosis of  
9 each patient and to appropriately risk stratify patients, ensuring the best individual  
10 management plan is decided upon. However, the stagnation in survival rate over recent  
11 decades suggests that staging accuracy, treatment selection and prognosis could be much  
12 improved. For example, lymph node metastases (LNMs) are one of the major prognostic  
13 indicators in esophageal cancer, but there is evidence that regional lymph node staging (N-  
14 stage) is presently suboptimal. [3, 4] Therefore, enhanced staging methods are required to  
15 improve prognostication and subsequent risk stratification of patients.

16

17 Esophageal cancer is typically confirmed by a small-sample biopsy taken during endoscopic  
18 examination. Despite advances in genomics, no molecular prognostic markers are currently  
19 in routine clinical use. [5] It has been proposed that additional tumour phenotype  
20 information may be derived by quantitative analysis of Positron Emission Tomography (PET)  
21 scans. [6] “Radiomics” broadly refers to automated, computerised and high-throughput  
22 extraction of quantitative image markers (features) from a large corpus of radiological  
23 images. [7] Radiomics features typically include histogram metrics (e.g. mean and  
24 maximum), shape descriptors (e.g. longest axis length and compactness) and textures (e.g.  
25 continuous length of voxels with similar intensities). [8] These features can be sensitive to  
26 differences in image parameters such as slice thickness. [9] Post-reconstruction  
27 harmonisation methods have been proposed to adjust for these differences, thus promoting  
28 standardised research between centres. [10]

29

30 The primary aim of this study was to test the generalizability of a UK single-centre  
31 esophageal cancer prognostic model incorporating radiomic features [11] firstly pre-  
32 harmonisation, then post-harmonisation, against a cohort of esophageal cancer patients  
33 treated exclusively with neo-adjuvant chemoradiotherapy (NACRT) according to the Dutch  
34 NACRT plus surgery versus surgery alone for oesophageal/junctional cancer (CROSS) trial  
35 regimen. [12] A widely generalizable prognostic model incorporating radiomic features of  
36 primary tumours might offer clinicians complimentary data beyond traditional prognostic  
37 factors that will assist treatment decision making and risk stratification. [11, 13] The  
38 secondary aim was to compare prognostic models with and without PET image features  
39 between cohorts to provide further validation.

40

41 **Materials & Methods**

42

43 This study was designed as a Transparent Reporting of a multivariate prediction model for  
44 Individual Prognosis Or Diagnosis (TRIPOD) type 3 external independent validation study.  
45 [14] A previously published prognostic model had been developed and internally validated  
46 in patients with esophageal cancer. Details of model development have been provided in  
47 Foley et al. [11] Briefly, the prognostic model had only been evaluated by same-centre

1 internal validation in patients managed by the South-East Wales Regional Upper  
2 Gastrointestinal (GI) Cancer Multi-Disciplinary Team (MDT), United Kingdom. A suitable  
3 independent cohort was not accessible at the time of publication. Institutional board review  
4 (IRB) approval was granted for the development of the prognostic model (REF  
5 14/WA/1208). The prognostic model was developed as part of a larger study investigating  
6 the prognostic significance of image texture analysis in gastro-oesophageal cancer (STAGE),  
7 and from here-on will be known as the STAGE cohort. The external validation cohort  
8 comprised patients treated with the CROSS regimen in The Netherlands. IRB permission was  
9 obtained for the external validation cohort.

## 10 Patient cohorts

11  
12  
13 In total, 449 patients were included in the development and validation of this prognostic  
14 model. Figure 1 details the number of patients in each cohort and the reasons for exclusion  
15 of patients from the CROSS validation cohort. The largest number of patient exclusions  
16 (n=23) from the CROSS cohort were because of the pre-defined metabolic tumour volumes  
17 (MTV) adopted in Foley et al [11] and used in this current study for consistency. A sensitivity  
18 analysis of these excluded cases has been included in Appendix B. Other main reasons for  
19 patient exclusion were different calibration units (n=11) and ATLAAS segmentation failure  
20 (n=7).

## 21 Primary Outcome

22  
23  
24 The primary endpoint of the published prognostic model is overall survival, defined as the  
25 number of months survived after the date of diagnosis until death or last day of follow-up.  
26 Dates of death were obtained from the Cancer National Information System Cymru (CaNISC)  
27 database (Velindre NHS Trust, Wales), reported by the Office for National Statistics. Dates of  
28 death of patients in the CROSS cohort were obtained from the national registry. In both  
29 cohorts, local researchers were not blinded to the dates of death. A uniform and  
30 standardised procedure for autosegmentation and radiomics computation was  
31 implemented at each centre to ensure consistent methodology.

## 32 Tumour Segmentation

33  
34  
35 Primary tumours were segmented on PET images using an automatic tree-based learning  
36 algorithm for advanced segmentation (ATLAAS). [15] The benefit of ATLAAS is that inter-  
37 observer variability in contouring is eliminated. Full details regarding the use of ATLAAS in  
38 this study are provided in Foley et al. and Berthon et al. [11, 15]

39  
40 The following model equation (Eq. 1) was used to calculate a prognostic score for each  
41 patient. This equation was derived using published methods. [16]

$$42$$
$$43 \text{ Prognostic score} = \text{Stage Group} * 0.397 - \text{Treatment} * 1.094 + \text{Age} * 0.024 - \log(\text{Histogram}$$
$$44 \text{ Energy}) * 1.320 + \log(\text{TLG}) * 1.748 + \text{Histogram Kurtosis} * 0.198$$

45 *Eq. 1*

## 46 External Validation

1  
2 The ATLAAS code and equations to calculate each of the PET image features were shared  
3 between institutions. The primary tumours on the PET scans of the CROSS patients were  
4 then segmented using ATLAAS and the MTVs produced were visually assessed for adequacy  
5 for quality control. Validation was firstly performed with pre-harmonisation metrics and  
6 then repeated with post-harmonisation PET features to adjust for potential differences  
7 between scanners. Fully anonymised data was then shared between institutions.

8  
9 Different PET/CT scanners and protocols were used across the cohorts (Appendix A). Radiomics  
10 features are known to change significantly as a function of scanner model, image acquisition or  
11 reconstruction settings, therefore we explored using the post-reconstruction Combat harmonisation  
12 method [17] to harmonise features extracted from images acquired across different scanners. Slice  
13 thickness was chosen for harmonisation because images from one scanner had different thickness  
14 values, which resulted in 5 categories (Appendix A, Table A.1). Further details of the cohorts,  
15 treatments received, PET/CT protocols, metric equations, variation in image features and  
16 the post-reconstruction PET harmonisation Combat method [17], used to adjust for batch  
17 effects across different datasets, have been provided in Appendix A.

## 18 19 Statistical analysis

20  
21 Categorical data are described as frequency (percent) and continuous variables as median  
22 (range) and differences assessed with appropriate non-parametric tests. There was no  
23 missing data in the development cohort and cases with missing data were excluded from  
24 the validation CROSS cohort. Patient characteristics at staging were compared for each  
25 cohort. Boxplots were generated locally on each cohort to compare the distributions of the  
26 model variables. Firstly, the published model was applied to 46 suitable patients in the  
27 CROSS cohort prior to PET harmonisation. A second model validation was then performed  
28 using image features calculated post-harmonisation. Model discrimination was evaluated  
29 using the log-rank test; a p-value of  $<0.05$  was defined as statistically significant. Model  
30 calibration followed a standard test procedure detailed in [18], and which has been  
31 previously implemented in [19]. In this study, we define model discrimination as preserved  
32 if the p-value of the calibration slope  $\beta = 1$  is  $>0.05$ . Thirdly, we performed the same  
33 validation steps for a prognostic model developed on the same STAGE cohort, but  
34 exclusively using clinical variables (age at diagnosis, stage and treatment) and no imaging  
35 based variables. Statistical analysis was performed with SPSS version 23.0 (IBM, Chicago,  
36 USA) and MATLAB version 9.0 (MathWorks, Natick, MA).

## 37 38 39 Results

40  
41 The baseline characteristics of the STAGE development, validation and CROSS cohorts are  
42 detailed in Table 1. The median overall survival of the CROSS cohort was 25 months (95%  
43 confidence interval (CI) 23.0 to 31.4). The median overall survival of the STAGE development  
44 and validation cohorts was 16.0 months (95% CI 13.8-18.2) and 14.0 months (95% CI 10.4-  
45 17.6), respectively.

46  
47 Boxplots were constructed to compare the values of log(TLG), log(Histogram Energy) and  
48 Histogram Kurtosis in between the STAGE and CROSS cohorts. (Fig. 2) Additional boxplots

1 and descriptive statistics of PET feature values pre- and post-harmonisation are included in  
2 Appendix B. There were similar mean values and distributions of the 3 variables between  
3 STAGE and CROSS cohorts, although a greater number of outliers were observed for  
4 Histogram Kurtosis in the STAGE cohort. This is probably due to a larger number of patients  
5 and greater range in MTV of the primary tumours included in the STAGE cohort. (Table B.1)

6  
7 A prognostic model containing clinical variables only was calculated from the STAGE  
8 development cohort using identical data from the original study. Age at diagnosis (HR  
9 1.025, 95% CI 1.011-1.040,  $p < 0.001$ ), stage (0.337, 0.243-0.468,  $p < 0.001$ ) and treatment  
10 (1.462, 1.187-1.802,  $p < 0.001$ ) were all independently and significantly associated with  
11 overall survival.

### 12 *Prognostic model developed by clinical and radiomic features*

#### 13 *Pre-harmonisation*

14  
15  
16  
17 Kaplan-Meier analysis did not demonstrate a significant difference in overall survival  
18 between patient quartiles in the CROSS cohort ( $\chi^2=1.27$ ,  $df=3$ ,  $p=0.74$ ). (Fig 3) The HRs of  
19 quartiles 2, 3 and 4 compared to quartile 1 was 0.89 (95% CI 0.29-2.75), 1.36 (95% CI 0.47-  
20 3.92) and 0.78 (95% CI 0.25-2.41), respectively. The calibration slope  $\beta$  of the prognostic  
21 score in the CROSS cohort was 1.09 (standard error (SE) 0.41).  $\beta$  is not significantly different  
22 from 1 ( $p=0.84$ ), which indicates that model discrimination is preserved.

23  
24 The mean overall survival for patient quartiles 1-4 were 34.0 months (95% CI 19.0-49.2),  
25 29.5 months (95% CI 19.5-39.5), 25.9 months (95% CI 14.8-37.0) and 41.2 months (95% CI  
26 25.9-56.4), respectively. Median overall survival could not be calculated for all quartiles. The  
27 median prognostic score for quartiles 1-4 was -0.51 ( $n=11$ , range -1.14 to -0.37), -0.15  
28 ( $n=11$ , range -0.36 to 0.01), 0.20 ( $n=11$ , range 0.04 to 0.30) and 0.48 ( $n=13$ , range 0.30 to  
29 1.16), respectively.

#### 30 *Post-harmonisation*

31  
32  
33 Following post-reconstruction PET harmonisation, repeated Kaplan-Meier analysis did not  
34 demonstrate a significant difference in overall survival between patient quartiles in the  
35 CROSS cohort ( $\chi^2=1.42$ ,  $df=3$ ,  $p=0.70$ ). (Fig 3) The HRs of quartiles 2, 3 and 4 compared to  
36 quartile 1 was 0.78 (95% CI 0.24-2.55), 1.47 (95% CI 0.50-4.25) and 1.15 (95% CI 0.39-3.40),  
37 respectively. The calibration slope  $\beta$  of the prognostic score in the CROSS cohort was 1.26  
38 (standard error (SE) 0.22).  $\beta$  is not significantly different from 1 ( $p=0.29$ ), which indicates  
39 that model discrimination is preserved. The adjusted survival data for the patient quartiles is  
40 available in Appendix B.

41  
42 These results indicate that PET harmonisation did not have a substantial effect on model  
43 validation, with similar results obtained using both methods.

### 44 *Prognostic model developed with clinical features only*



1 The median prognostic score of the model developed with clinical variables only was -2.68  
2 (range -4.89 to -0.17). As shown in Figure 4, Kaplan-Meier analysis did not demonstrate a  
3 significant difference in overall survival between patient quartiles in the CROSS cohort  
4 ( $X^2=1.19$ ,  $df=3$ ,  $p=0.75$ ). The HRs of quartiles 2, 3 and 4 compared to quartile 1 was 0.93  
5 (95% CI 0.27-3.23), 1.41 (95% CI 0.45-4.43) and 1.53 (95% CI 0.51-4.57), respectively. The  
6 calibration slope  $\beta$  of the prognostic score in the CROSS cohort was 2.15 (SE 0.72).  $\beta$  is not  
7 significantly different from 1 ( $p=0.29$ ), which indicates that model discrimination is  
8 preserved.

9  
10 In the prognostic model with clinical variables only, patients in quartiles 2 & 3 were  
11 combined to create an intermediate risk group, following a previously published method.  
12 [20] (Fig. 5) Applying Bonferroni correction, there was no statistically significance difference  
13 between the low, intermediate and high risk groups ( $X^2$  0.712,  $df$  2,  $p=0.701$ ) but a  
14 separation in overall survival curves was observed (intermediate risk vs low risk HR 1.16  
15 (95% CI 0.41-3.30 and high risk vs low risk HR 1.53 (95% CI 0.51-4.58)). The calibration slope  
16  $\beta=$  2.15 (SE .72,  $p$ -value 0.29) indicating model discrimination was preserved.

## 17 **Discussion**

18  
19  
20 Patients with esophageal cancer have a poor prognosis and the incidence of the disease is  
21 increasing. [21] Despite advances in modern healthcare, survival rates remain low.  
22 Enhanced staging algorithms are required to improve the accuracy of staging, which informs  
23 clinicians of the likely prognosis and provides subsequent patient risk stratification.  
24 Prognostic models incorporating radiomic features are one strategy being investigated for  
25 this purpose.

26  
27 This external validation study has shown that results of a developed prognostic model  
28 combining clinical risk factors and PET radiomics features was not replicated in a cohort of  
29 patients treated with the CROSS trial regimen. However, when a prognostic model including  
30 only clinical variables from the STAGE development cohort was tested, some aspects of the  
31 model were indicative of transferability to the CROSS cohort. Our data shows that clinical  
32 features of esophageal cancer remain prognostic across different countries and studies.

33  
34 Despite not being able to replicate the validation results of the published prognostic model,  
35 this study remains clinically important because more accurate staging of esophageal cancer  
36 is essential to improve survival rates. Validated prognostic and predictive radiomics models  
37 are one strategy to improve radiological staging of esophageal cancer. [22] Greater staging  
38 accuracy will improve patient risk stratification, which is critically important for optimising  
39 personalised treatment decision-making. Once validated, staging algorithms incorporating  
40 radiomics may enable clinicians to decide upon the best management plan from the outset  
41 of diagnosis, therefore providing the greatest chance of survival for each patient.

42  
43 A number of important methodological reasons in the modelling process may have  
44 contributed to the lack of external validity of the prognostic model when transported to the  
45 CROSS observations. First, the PET image acquisition protocols in the CROSS regimen cohort  
46 may not have been as strictly policed as in the STAGE study, leading to divergence in PET  
47 acquisition parameters. (Table A.1) All patients in STAGE ( $n=403$ ) were staged using the

1 same PET/CT scanner and protocol. However, different PET/CT scanners and protocols were used  
2 in both the STAGE and CROSS cohorts. Harmonising PET image features demonstrated little  
3 improvement in the model validity between cohorts.

4  
5 Harmonising PET image features demonstrated little improvement in the model validity  
6 between cohorts, which supports this post-reconstruction method in external validation  
7 radiomics studies and suggests that harmonisation had little influence in these cohorts.  
8 These findings contradict those of Orhac et al. [10] Several factors could explain the lack of  
9 effect. The clinical variables of patient age, TNM stage and treatment are likely to have the  
10 greatest impact on overall survival compared to the image features. The PET features used  
11 in the original model by Foley et al (TLG, Histogram Energy and Histogram Kurtosis) were  
12 not investigated in Orhac et al. Furthermore, although the Combat algorithm has been used  
13 in genomics, it has not yet been validated in radiomics. A consensus on uniformly  
14 standardised PET imaging protocols is required for multi-institutional validation of  
15 prognostic/predictive models incorporating radiomics. [23]

16  
17 Second, the prognostic model excluded patients with small MTV < 5 mL, thus further  
18 reducing the number of CROSS patients that were eligible for validation. The small patient  
19 numbers in the external validation cohort limits the ability to replicate the results of the  
20 STAGE prognostic model. This study is likely to be under-powered and improved validation  
21 could be achieved by increasing the cohort size. Patients with a smaller MTV were more  
22 likely to be suitable for radical therapy and therefore eligible for recruitment into the CROSS  
23 trial. When the excluded small MTV cases were tested in the sensitivity analysis included in  
24 Appendix B, no significant difference in overall survival between patient quartiles remained  
25 ( $X^2=3.85$ ,  $df=3$ ,  $p=0.28$ ). In addition, evidence at the time of prognostic model development  
26 suggested possible unstable segmentation at smaller MTVs and an increase in redundant  
27 (highly cross-correlated) radiomic data that can be extracted. [24] There is no clear  
28 consensus on minimum MTV in PET radiomics studies. One study recommends excluding  
29 MTVs of < 45 mL, although only one calculation choice for local entropy, despite the many  
30 possibilities of discretisation steps and matrices available, was evaluated in this study. [25]  
31 Other studies have previously recommend excluding patients with a primary MTV of < 10  
32 mL. [26, 27] However, prognostic models including image features extracted from small  
33 tumour volumes can still be developed. [8] The original model by Foley et al. did not  
34 examine a wide range of higher order features, some of which may have turned out  
35 reproducible and significantly prognostic with the expanded dataset. However, since the  
36 scope of this study was only the feasible generalizability of the original model, we did not  
37 re-analyse using additional textural features. The possibility for including redundant data  
38 exists but providing the study is appropriately powered, the model can still be compared to  
39 those containing only clinical variables.

40  
41 Third, the development of the previous prognostic model did not include an exhaustive  
42 radiomic feature selection steps to identify features that would be robustly reproducible  
43 within the STAGE cohort and hence more likely to be transferable to the CROSS cohort. [8]  
44 Details of the PET variables implemented in the developed prognostic model can be found  
45 in Foley et al. [11] These variables were shown to have prognostic significance in the early  
46 radiomics literature [28-30] and were implemented identically.

1 More studies are required to test the reliability, robustness and additional value of PET  
2 image features across a range of MTVs and between different PET/CT scanners. [9, 26]  
3 Regarding the original model, TLG and Histogram Energy have shown good reproducibility  
4 results, however there is mixed evidence for Histogram Kurtosis. [31] Previous studies have  
5 found significant associations between higher order features and overall survival [29] and  
6 that the amount of complementary radiomic information gained increases with larger  
7 MTVs. [26] Despite this, the original development study did not demonstrate prognostic  
8 significance of any higher order features, although only 3 such features were investigated.  
9

10 Advanced correction algorithms are being developed to harmonise features extracted from  
11 scans with different acquisition parameters, which could greatly benefit multi-centre  
12 radiomic studies and reduce variation in metrics. [32]  
13

14 Standardisation efforts such as the Image Biomarker Standardisation Initiative (IBSI) [33] are  
15 an important methodological step towards reducing sensitivity of radiomic features to  
16 computation (image extraction) software. Deployment of the same autosegmentation tool  
17 (ATLAAS [15]) reduced inter-observer variability in contouring and the same feature  
18 extraction software that was executed locally was used in both participating centres. These  
19 techniques are examples of standardised processes that improve the robustness of radiomic  
20 features.  
21

22 Lastly, a relatively small proportion of the STAGE cohort received NACRT or surgery alone  
23 (Table 1). These differences may not have been adjusted for completely by the original  
24 model multivariate regression. The STAGE cohort is relatively heterogeneous cohort of  
25 patients compared to the CROSS cohort, because it was collected during an observational  
26 cohort study recruiting all patients with esophageal cancer. Patients in the CROSS cohort  
27 were all treated with NACRT, so they share more similar characteristics. Differences  
28 between validation cohorts are important in external validation studies because the  
29 generalisation of the model can be tested at its extremes. Furthermore, this points the way  
30 forward to improved (reproducible) feature selection methodology and updating of the  
31 original model to address a more generalized clinical question.  
32

33 All prognostic models must be validated in an independent external cohort before being  
34 considered for use in clinical practice because many models present optimistic and over-  
35 fitted results from development cohorts. [34] However, external validation studies are  
36 rarely performed. A review of the performance of prognostic models showed that 11% are  
37 externally validated. [35] This may explain why few developed prognostic models are  
38 adopted into clinical practice. [36] Our collaborative research group is planning to update  
39 this prognostic model and perform a further external validation study with more robust  
40 feature selection and standardised feature extraction algorithms using all tumour volumes.  
41

42 In conclusion, this initial TRIPOD type 3 external validation study evaluated a prognostic  
43 model developed in esophageal cancer patients staged with PET/CT. The prognostic model  
44 did not enable significant discrimination between patient risk groups in the CROSS cohort,  
45 but a second model including clinical variables only (age, disease stage and treatment)  
46 demonstrated transferable prognostic factors between international cohorts.  
47

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5 Emission Tomography Imaging Centre (PETIC) in Cardiff and members of the South-East  
6 Wales Upper GI Cancer MDT committee.

7

8

9 **Ethical Statement**

10 Institutional review board approval was obtained.

11

12 **Data Availability**

13 The data that has been used in this study is confidential and cannot be shared

14

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17

18 **Competing interests**

19 The authors declare that they have no competing interests.

20

21 **Author contributions**

22 KF, AR, LW and ES conceived and designed the study. RL, MB, MS, PK and TC collected the  
23 data. ZS, PW, CP and PK preformed the data analysis. KF, LW, JS, TC and AD drafted the  
24 manuscript. All authors read and approved the final manuscript.

25

26

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## Tables

Table 1. Baseline Characteristics of Patients in Development, Validation and CROSS Cohorts

Frequency (%)	STAGE Development Cohort (n=302)	STAGE Validation Cohort (n=101)	CROSS cohort (n= 46)	p-value*
Median Age	67.0 years (Range 39-83)	69.0 years (Range 39-84)	64.5 years (Range 47-77.8)	0.114
Gender (M: F)	227 (75.2): 75 (24.8)	78 (77.2): 23 (22.8)	38 (82.6): 8 (17.4)	0.528
Histology				0.602
Adeno	237 (78.5)	79 (78.2)	39 (84.8)	
SCC	65 (21.5)	22 (21.8)	7 (15.2)	
Tumour Location				0.010
Oesophagus	192 (63.6)	47 (46.5)	28 (60.9)	
Gastro-oesophageal junction	110 (36.4)	54 (53.5)	18 (39.1)	
Stage Groups				0.018
Stage 1	17 (5.6)	2 (2.0)	2 (4.4)	
Stage 2	56 (18.5)	24 (23.8)	10 (21.7)	
Stage 3	160 (53.1)	57 (56.4)	33 (71.7)	
Stage 4	69 (22.8)	18 (17.8)	1 (2.2)	
Treatment				<0.001
Curative	158 (52.3)	50 (49.5)	46 (100)	
SA	24 (15.2)	4 (8.0)	0 (0.0)	
NACT	67 (42.4)	23 (46.0)	0 (0.0)	
NACRT	13 (8.2)	7 (14.0)	46 (100)	
dCRT	54 (34.2)	16 (32.0)	0 (0.0)	
Palliative	144 (47.7)	51 (50.5)	0 (0.0)	
Overall Survival				<0.001
Alive	70 (23.2)	43 (42.6)	20 (43.5%)	
Dead	232 (76.8)	58 (57.4)	26 (51.5%)	

SCC squamous cell carcinoma; SA surgery alone; NACT neo-adjuvant chemotherapy; NACRT neo-adjuvant chemoradiotherapy; dCRT definitive chemoradiotherapy; \*chi-square test



## Figure Legends

Figure 1. Study flowchart describing the numbers of patients in each cohort and reasons for exclusions from the CROSS cohort.

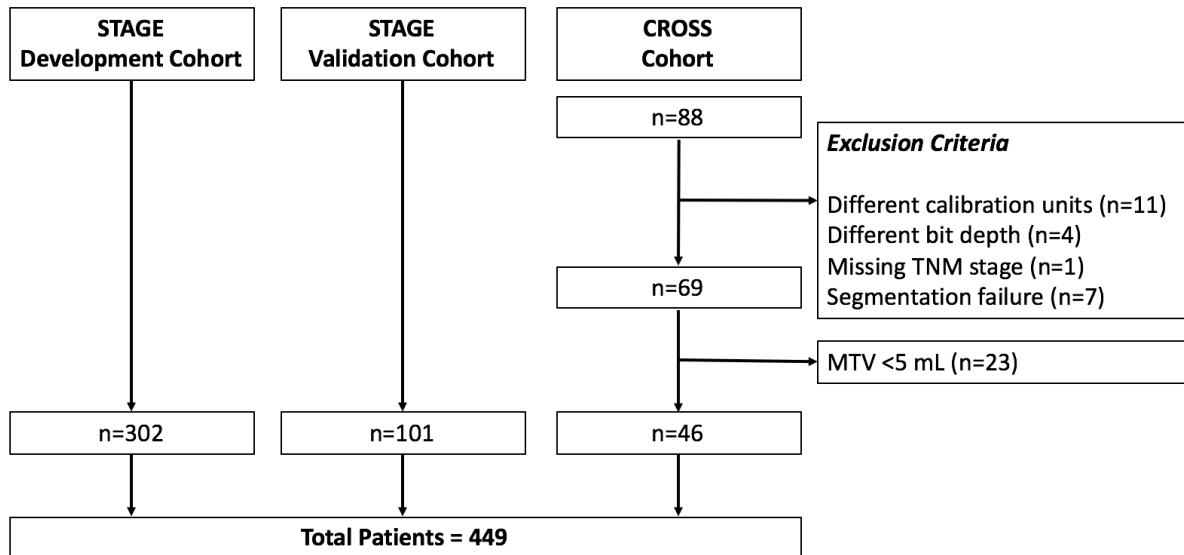


Figure 2. Boxplots displaying pre-harmonisation mean values and interquartile ranges of log(TLG), log(Histogram Energy) and Histogram Kurtosis in STAGE and CROSS cohorts.

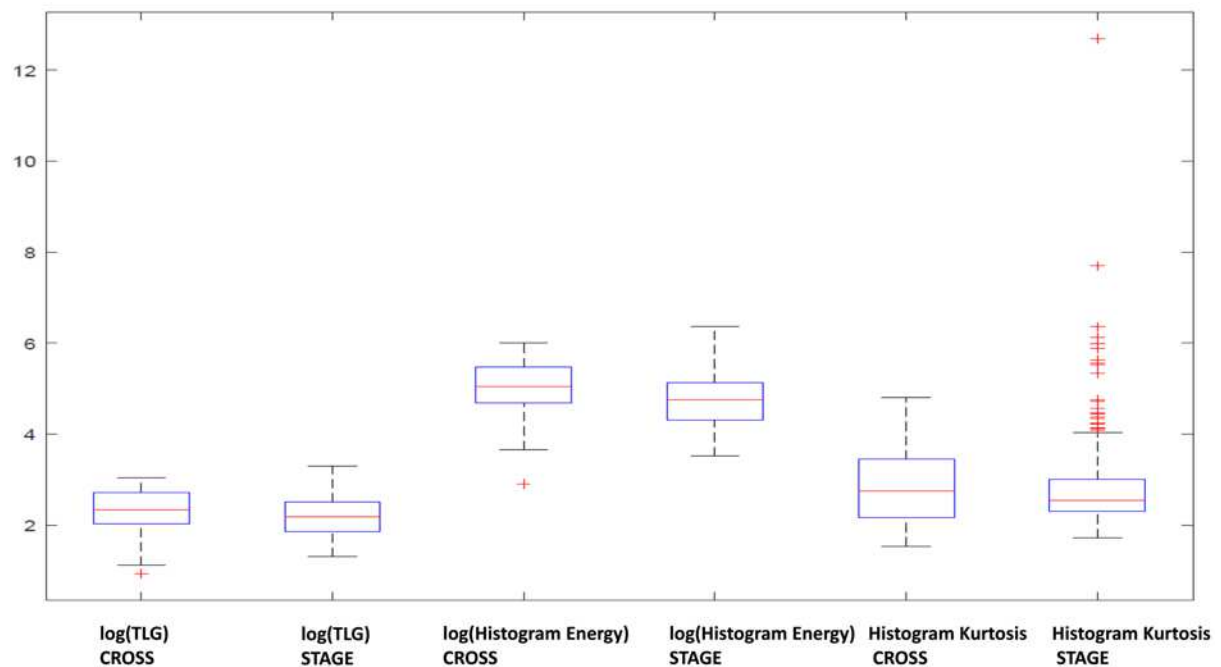


Figure 3. Cumulative survival curves of patient quartiles (Q1-4) in CROSS cohort using model developed with clinical and radiomic features ( $\chi^2=1.27$ ,  $df=3$ ,  $p=0.74$ ).

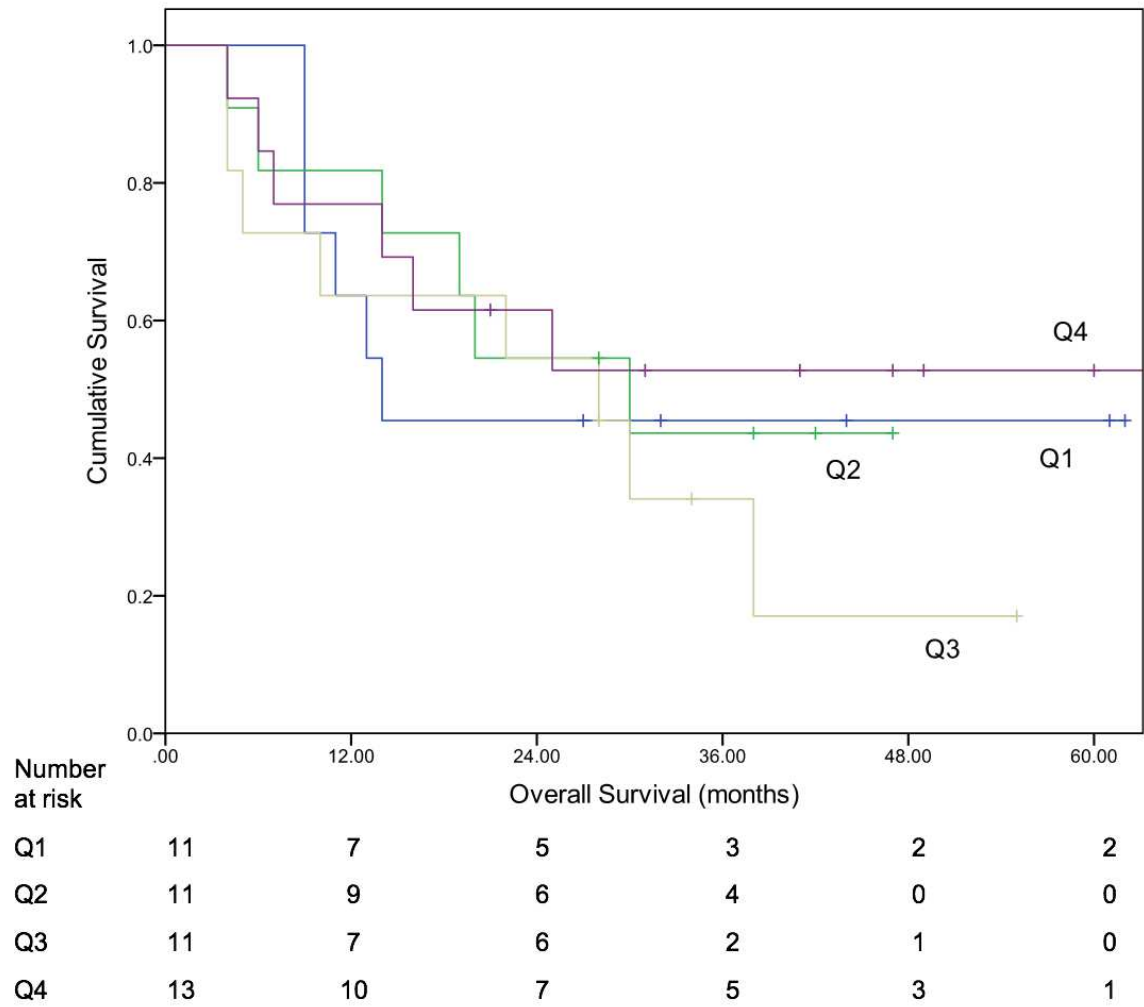
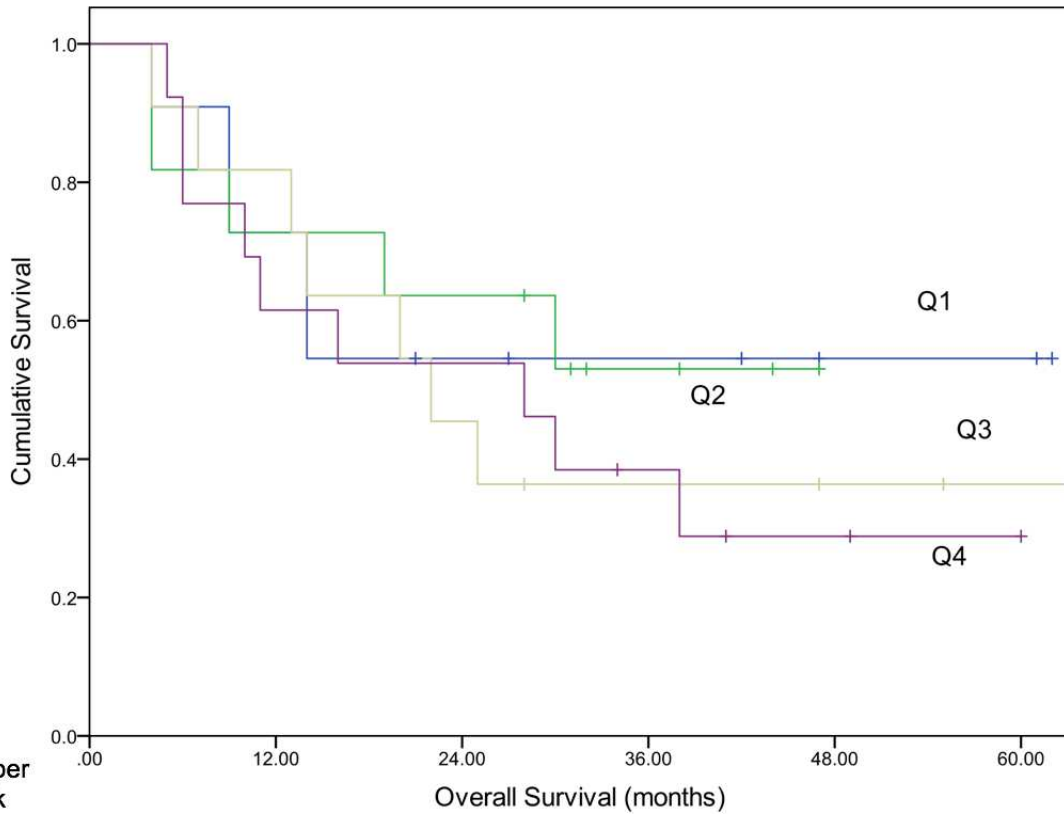


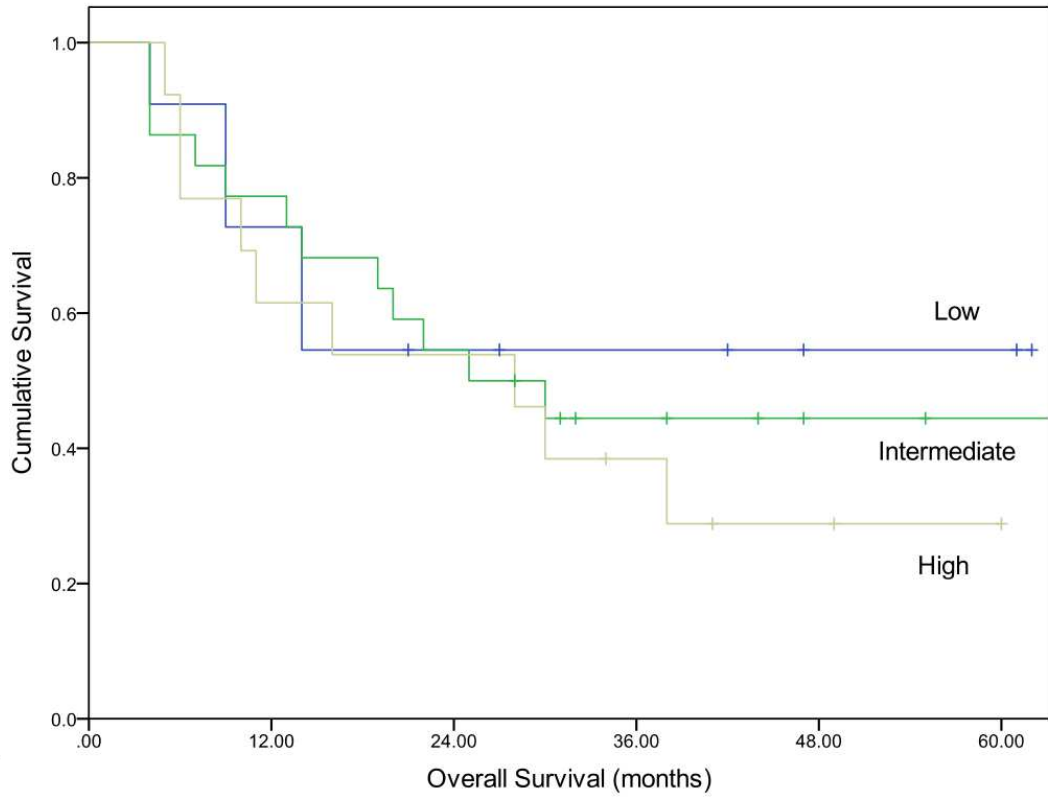
Figure 4. Cumulative survival curves of patient quartiles (Q1-4) in CROSS cohort using model developed with clinical features only ( $\chi^2=1.19$ ,  $df=3$ ,  $p=0.75$ ).



Number  
at risk

	0.00	12.00	24.00	36.00	48.00	60.00
Q1	11	8	6	6	6	6
Q2	11	8	7	6	6	6
Q3	11	9	5	4	4	4
Q4	13	8	7	5	4	4

Figure 5. Cumulative survival curves of combined risk groups in CROSS cohort using model developed with clinical features only. The original quartile 1 corresponds to the low-risk group, quartiles 2 & 3 were combined to create an intermediate risk group and quartile 4 corresponds to the high-risk group.



	Overall Survival (months)					
Number at risk	0	12	24	36	48	60
Low	10	8	5	3	2	2
Intermediate	21	17	12	6	2	1
High	12	8	7	4	2	0