

Machine learning to predict early recurrence after oesophageal cancer surgery

S. A. Rahman¹ , R. C. Walker¹, M. A. Lloyd¹, B. L. Grace¹, G. I. van Boxel⁹, B. F. Kingma⁹, J. P. Ruurda⁹, R. van Hillegersberg⁹, S. Harris², S. Parsons³, S. Mercer⁴, E. A. Griffiths⁵, J. R. O'Neill⁶, R. Turkington⁸, R. C. Fitzgerald⁷ and T. J. Underwood¹, on behalf of the OCCAMS Consortium*

¹Cancer Sciences Unit and ²Department of Public Health Sciences and Medical Statistics, University of Southampton, Southampton, ³Department of Surgery, Nottingham University Hospitals NHS Trust, Nottingham, ⁴Department of Surgery, Portsmouth Hospitals NHS Trust, Portsmouth, ⁵Department of Upper Gastrointestinal Surgery, University Hospitals Birmingham NHS Foundation Trust, Birmingham, ⁶Cambridge Oesophagogastric Centre, Addenbrookes Hospital, Cambridge University Hospitals Foundation Trust, and ⁷Hutchison/Medical Research Council Cancer Unit, University of Cambridge, Cambridge, and ⁸Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, UK, and ⁹Department of Surgery, University Medical Centre, Utrecht, the Netherlands

Correspondence to: Professor T. J. Underwood, Cancer Sciences Unit, University of Southampton, Tremona Road, Southampton SO16 6YD, UK (e-mail: tju@soton.ac.uk;  @TimTheSurgeon, @SaqRahman, @Robwalker27, @uoscares, @HeartburnCancer)

Background: Early cancer recurrence after oesophagectomy is a common problem, with an incidence of 20–30 per cent despite the widespread use of neoadjuvant treatment. Quantification of this risk is difficult and existing models perform poorly. This study aimed to develop a predictive model for early recurrence after surgery for oesophageal adenocarcinoma using a large multinational cohort and machine learning approaches.

Methods: Consecutive patients who underwent oesophagectomy for adenocarcinoma and had neoadjuvant treatment in one Dutch and six UK oesophagogastric units were analysed. Using clinical characteristics and postoperative histopathology, models were generated using elastic net regression (ELR) and the machine learning methods random forest (RF) and extreme gradient boosting (XGB). Finally, a combined (ensemble) model of these was generated. The relative importance of factors to outcome was calculated as a percentage contribution to the model.

Results: A total of 812 patients were included. The recurrence rate at less than 1 year was 29.1 per cent. All of the models demonstrated good discrimination. Internally validated areas under the receiver operating characteristic (ROC) curve (AUCs) were similar, with the ensemble model performing best (AUC 0.791 for ELR, 0.801 for RF, 0.804 for XGB, 0.805 for ensemble). Performance was similar when internal–external validation was used (validation across sites, AUC 0.804 for ensemble). In the final model, the most important variables were number of positive lymph nodes (25.7 per cent) and lymphovascular invasion (16.9 per cent).

Conclusion: The model derived using machine learning approaches and an international data set provided excellent performance in quantifying the risk of early recurrence after surgery, and will be useful in prognostication for clinicians and patients.

*Members of the OCCAMS Consortium are co-authors of this study and are listed in *Appendix S1* (supporting information)

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Introduction

Oesophageal adenocarcinoma carries a poor prognosis. Among the less than 40 per cent of patients who are

candidates for curative treatment¹, the 5-year survival rate remains approximately 25–50 per cent in randomized trials^{2–4} and rarely exceeds 50 per cent in case series.

Early recurrence (less than 1 year) after surgery is a feared outcome, with rates of 20–30 per cent frequently reported^{3–5}, despite the increasing uptake of neoadjuvant chemotherapy (NACT) and neoadjuvant chemoradiotherapy (NACRT). This is of particular concern because recovery from oesophagectomy is often long and the risk of major complications (Clavien–Dindo grade III–V) is as high as 30 per cent⁶. Many patients have not recovered from the primary cancer treatment when they experience recurrence.

In an ideal setting, prediction of early recurrence before embarking on a multimodal surgical pathway would provide useful information for patients and clinicians. However, staging information correlates poorly between preoperative and postoperative settings⁷, and genomic information is not yet able to predict outcome. Even the most robust preoperative models for prediction have a modest performance at best⁸. In contrast, postoperative information, although not able to influence surgical treatment decisions, is more prognostic and potentially informative for patients. It may also be helpful in making decisions on the merits of adjuvant therapy, further refining the high-risk group of patients in whom novel adjuvant treatments are currently being considered.

Naive logistic regression has been the dominant approach to binary outcome prediction in clinical medicine for decades. Adoption of modern modified regression and machine learning techniques has been limited, in part owing to concerns over computational complexity and reliability. However, an increasing body of evidence has demonstrated that they outperform traditional techniques in predictive performance^{9,10}, although this is debatable¹¹. In part, the appeal of these approaches lies in their ability to model complex non-linear relationships that are common in cancer data, and which are challenging to model effectively with logistic/linear approaches. The increasing accessibility of software design now also allows the relatively straightforward deployment of these black-box techniques.

The Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) Consortium¹² previously published a multicentre UK cohort study that assessed survival according to Mandard Tumour Regression Grade (TRG)¹³. This study included patients who had undergone oesophagectomy for adenocarcinoma of the oesophagus or gastro-oesophageal junction (GOJ) preceded by NACT. A clinically meaningful response to NACT was limited to TRG 1–2 only, which represented approximately 15 per cent of patients. The present study used this database, supplemented with an international cohort from the Netherlands, and machine learning techniques to develop

and validate a clinically useful predictive model for early recurrence in oesophageal adenocarcinoma.

Methods

The OCCAMS Consortium is a UK-wide multicentre consortium set up to facilitate clinical and molecular stratification of oesophagogastric cancer. It has ethical approval for biological sample collection and analysis in conjunction with detailed clinical annotation (Research Ethics Committee number 10/H0305/1). Data collection and participation in research were approved by institutional ethics committees at each OCCAMS site and University Medical Centre (UMC) Utrecht.

Source of data

Data were sourced from six tertiary oesophagogastric centres in the UK, as described previously¹². Briefly, the records of consecutive patients from each centre who underwent a planned curative oesophagectomy for adenocarcinoma between 2000 and 2013, and also received NACT (platinum-based triplet or cisplatin and 5-fluorouracil) were reviewed and collated. Treatment was decided by a multidisciplinary team at individual institutions. Neoadjuvant treatment was considered for patients with locally advanced (cT2+) or node-positive disease according to local and national guidelines. Clinical, pathological, recurrence and survival data were recorded. Data from one of the original centres were incomplete to the extent that modelling could not take place and were excluded *a priori*. To include NACRT as a factor in the model, further patients were identified from University Hospitals Southampton and UMC Utrecht, where CROSS (Chemoradiation for Oesophageal Cancer Followed by Surgery Study)-type NACRT⁴ has been the standard of care for oesophageal adenocarcinoma for a number of years. Patients whose tumours were deemed unresectable at the time of surgery or who had metastatic disease on post-operative histology (pM1) were excluded from the analysis.

The primary outcome measure was early recurrence, defined as confirmed local, regional or distant recurrence at less than 1 year from the date of surgery^{5,8,14}. Missing data were treated as being missing completely at random and handled by listwise deletion. Modelling was based on a complete-case analysis.

Predictor characteristics

Univariable statistics were calculated using non-parametric Mann–Whitney *U* and χ^2 tests. The predictive models were generated on the whole data set. All available variables were included in the analysis. A circumferential resection margin (CRM) of less than 1 mm was considered to

be involved (and hence R1), in accordance with Royal College of Pathologists (RCP) guidelines¹⁵. Tumour grade and TRG¹³ were assessed by dedicated gastrointestinal histopathologists who were blinded to the clinical data. TRG was used to distinguish between responders (TRG 1–2) and non-responders (TRG 3–5), in line with the previous publication based on this data set¹². To increase the yield of information from lymph node data, both the number of positive lymph nodes and total lymph node harvest were considered as absolute numbers. For the regression model, linearity was assumed for continuous variables. The variables used to predict outcome were: age, sex, tumour location, type of neoadjuvant therapy, response to neoadjuvant therapy (TRG), ypT category, lymphovascular invasion, completeness of resection, grade of differentiation, number of positive lymph nodes and total number of lymph nodes examined.

Model building and validation

Elastic net regularized logistic regression (ELR)¹⁶ was used along with two machine learning techniques: random forest (RF)¹⁷ and extreme gradient boosting (XG boost, XGB)¹⁸. ELR applies a combination of the ridge and lasso penalties^{19,20} with the benefits of both (partly minimization of overfitting and variable selection). RF combines a specified number of decision trees (typically around 1000) created on random subsets of the data set, and is probably the most widely used machine learning approach in the medical literature. XGB attempts to improve sequentially by generating models to explain where the original model fails and then repeating this process (typically around 1000 times), while simultaneously applying regularization to minimize overfitting. Having generated individual models, these were combined to generate overall predictions²¹, an approach that theoretically is particularly beneficial when using diverse model types (such as those described above) that capture different elements of patients' risk profiles.

For ELR, the optimal α and λ hyperparameters (penalty severities) were selected by grid search using tenfold cross-validation with five repeats during model generation and log loss as the metric for optimization. The RF model was derived from 1000 decision trees and hyperparameter tuning was conducted in a similar fashion (for number of variables per tree, split rule and minimum node size). The XGB model was again derived by cross-validation of hyperparameters (number of optimization rounds, maximum tree depth, minimum weight in each child node, minimum loss reduction (γ), regularization penalty (η) and subsampling for regularization). Full details of hyperparameter tuning are available in *Appendix S2* (supporting

information). These three models were then combined to generate the final (ensemble) model by generating a linear blend of predicted probabilities using logistic regression.

Discrimination of the models was assessed using the area under the receiver operator characteristic (ROC) curve (AUC). In the context of this paper, if two random patients were selected, one with recurrence of cancer at less than 1 year and one disease-free at 1 year, the AUC is equivalent to the probability the model will score the patient with recurrence higher than the patient without. Internal validation was performed using 0.632 bootstrapping, with 1000 resampled data sets. Bootstrapping was preferred for internal validation over splitting the cohort into derivation and validation sets, as this has been shown to reduce bias and improve overall model performance, particularly with moderately sized data sets^{22–24}. Calibration was assessed visually and formally with the Hosmer–Lemeshow test. As the data set contains multiple centres with small numbers of patients, an internal–external validation procedure was opted for, as advocated by Steyerberg and Harrell²⁵. This entails generating models on all centres apart from one and validating the model on the remaining centre. This process is then repeated leaving each centre out sequentially, and a mean calculated. This method demonstrates how the model performs in external data while also allowing the whole data set to be used for training.

Unadjusted tree models (such as RF, which is included in the ensemble model) and other maximum margin methods typically calibrate poorly as a consequence of their methodology, with predicted probabilities biased towards the centre. To allow meaningful interpretation of probability, isotonic regression was used to scale probabilities on the final model, as described previously^{26,27}.

In contrast to logistic regression, assessing global variable importance is challenging using machine learning techniques and to an extent they are black boxes. As coefficients, as seen in logistic regression, are not used, an alternative method is required. The VarImp function of the caret R package was used, where ROC curves are generated for the outcome for each individual predictor, and the contribution to the global ROC curve calculated as a percentage. Owing to the nature of higher-order interactions present in the model, variable importance in individual predictions must be calculated independently. The mean marginal contribution of each variable was calculated (change from the mean prediction; Shapley value²⁸) for individual predictions. A similar approach was used by Nanayakkara and colleagues²⁹ for analysing in-hospital mortality following cardiac arrest.

Data analysis was conducted using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Fig. 1 Study flow diagram

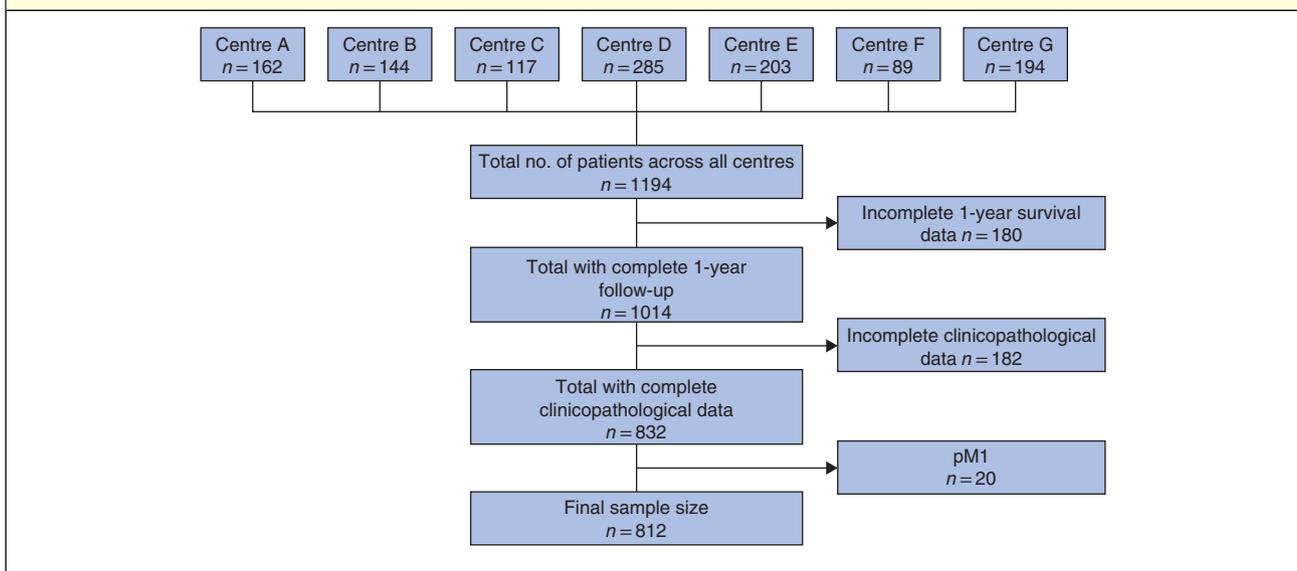


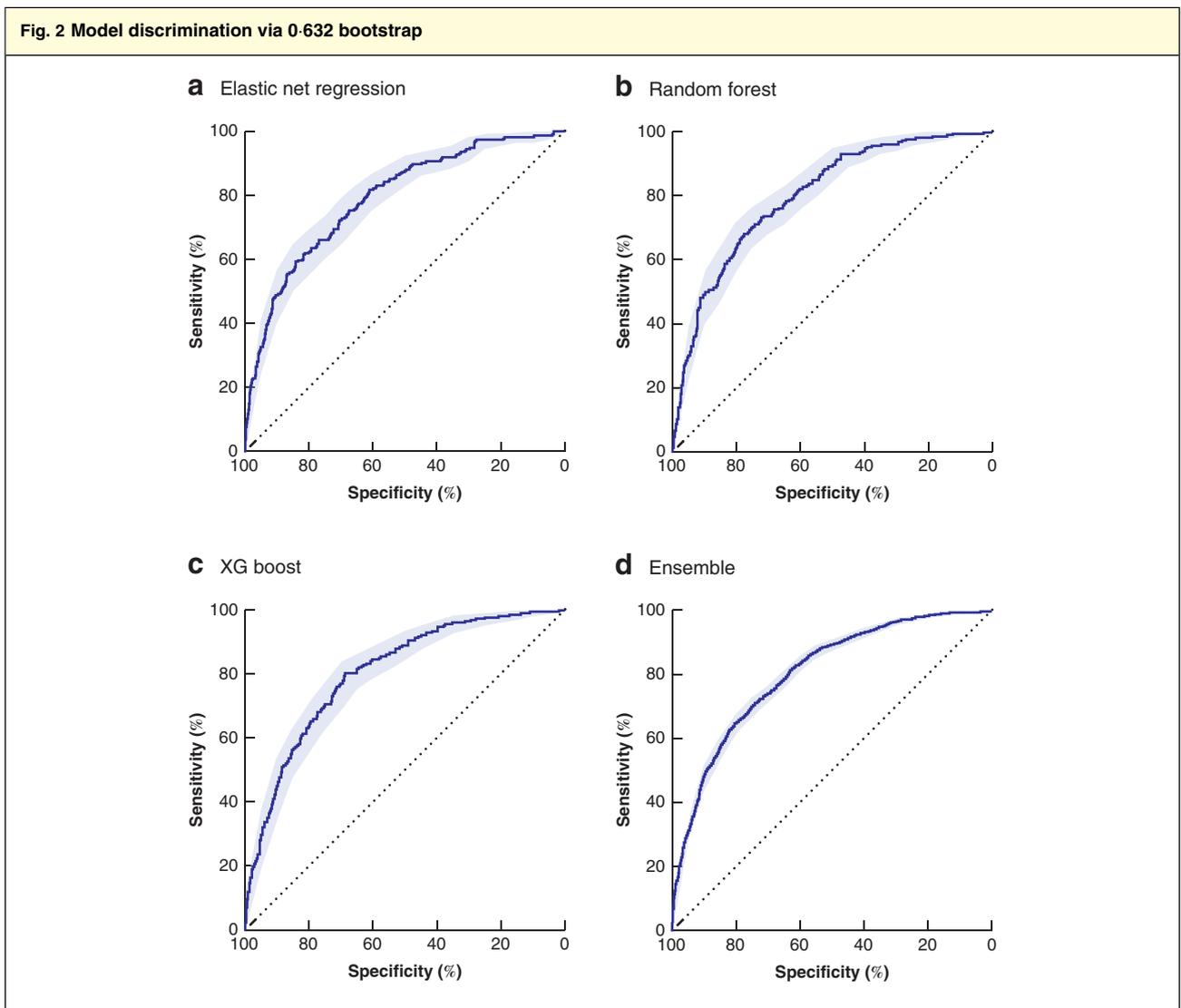
Table 1 Clinicopathological data for whole cohort and according to early recurrence

| | All patients (n = 812) | No early recurrence (n = 576) | Early recurrence (n = 236) | P† |
|---------------------------------------|------------------------|-------------------------------|----------------------------|----------|
| Age (years)* | 64.0 (28–83) | 63.9 (28–81) | 64.1 (38–83) | 0.855§ |
| Sex ratio (M : F) | 687 : 125 | 487 : 89 | 200 : 36 | 0.944 |
| Tumour site | | | | 0.352 |
| Oesophagus | 361 (44.5) | 250 (43.4) | 111 (47.0) | |
| GOJ | 451 (55.5) | 326 (56.6) | 125 (53.0) | |
| Tumour Regression Grade | | | | < 0.001 |
| TRG 1–2 | 145 (17.9) | 125 (21.7) | 20 (8.5) | |
| TRG 3–5 | 667 (82.1) | 451 (78.3) | 216 (91.5) | |
| ypT category | | | | < 0.001 |
| ypT0 | 33 (4.1) | 28 (4.9) | 5 (2.1) | |
| ypT1 | 96 (11.8) | 87 (15.1) | 9 (3.8) | |
| ypT2 | 141 (17.4) | 125 (21.7) | 16 (6.8) | |
| ypT3 | 495 (61.0) | 320 (55.6) | 175 (74.2) | |
| ypT4 | 47 (5.8) | 16 (2.8) | 31 (13.1) | |
| No. of positive LNs* | 1 (0–41) | 0.5 (0–30) | 4 (0–41) | < 0.001§ |
| ypN > 0 | 495 (61.0) | 288 (50.0) | 207 (87.7) | < 0.001 |
| Total no. of lymph nodes* | 24 (0–75) | 24 (0–75) | 23 (6–61) | 0.805§ |
| > 15 | 688 (84.7) | 481 (83.5) | 207 (87.7) | 0.134 |
| Lymphovascular invasion | 372 (45.8) | 202 (35.1) | 170 (72.0) | < 0.001 |
| R1 resection | 231 (28.4) | 118 (20.5) | 113 (47.9) | < 0.001 |
| Tumour grade (differentiation) | | | | < 0.001 |
| Well | 63 (7.8) | 55 (9.5) | 8 (3.4) | |
| Moderate | 300 (36.9) | 233 (40.5) | 67 (28.4) | |
| Poor/anaplastic | 449 (55.3) | 288 (50.8) | 161 (68.2) | |
| Neoadjuvant treatment | | | | 0.061 |
| NACT | 657 (80.9) | 476 (82.6) | 181 (76.7) | |
| NACRT | 155 (19.1) | 100 (17.4) | 55 (23.3) | |

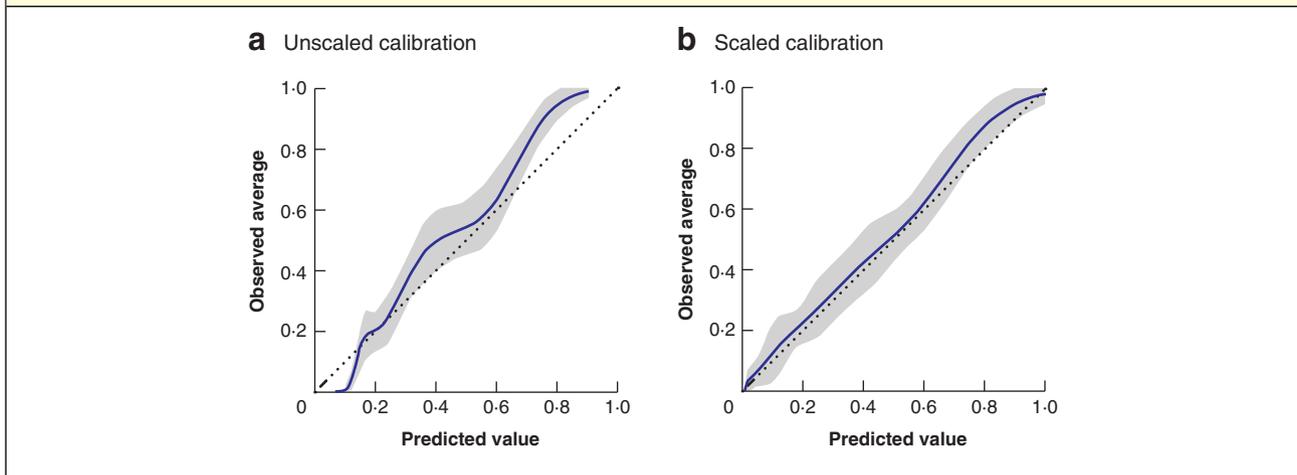
Values in parentheses are percentages unless indicated otherwise; *values are median (range). GOJ, gastro-oesophageal junction; LN, lymph node; NACT, neoadjuvant chemotherapy; NACRT, neoadjuvant chemoradiotherapy. † χ^2 test, except ‡Mann–Whitney *U* test.

| | Area under the curve | | |
|------------------------|----------------------|----------------------|------------------------------|
| | Apparent | Internal validation | Internal-external validation |
| Elastic net regression | 0.805 (0.772, 0.838) | 0.791 (0.757, 0.826) | 0.798 (0.713, 0.883) |
| Random forest | 0.980 (0.972, 0.987) | 0.801 (0.769, 0.834) | 0.805 (0.721, 0.889) |
| XG boost | 0.849 (0.822, 0.877) | 0.804 (0.772, 0.836) | 0.800 (0.716, 0.883) |
| Ensemble | 0.902 (0.881, 0.992) | 0.805 (0.790, 0.819) | 0.804 (0.721, 0.887) |

Values in parentheses are 95 per cent confidence intervals.



Receiver operating characteristic (ROC) curves for **a** elastic net regression (area under the curve (AUC) 0.791, 95 per cent c.i. 0.757 to 0.826), **b** random forest (AUC 0.801, 0.769 to 0.834), **c** XG boost (AUC 0.804, 0.772 to 0.836) and **d** ensemble (AUC 0.805, 0.790 to 0.819). The shaded area represents the 95 per cent confidence interval.

Fig. 3 Ensemble model calibration before and after adjustment

a Unscaled calibration (intercept 0.395, slope 1.574) and **b** scaled calibration (intercept 0.143, slope 0.988). The shaded area represents two standard errors.

Table 3 Variable importance

| | Importance (%) | | | |
|------------------------------------|------------------------|---------------|----------|------------------------|
| | Elastic net regression | Random forest | XG boost | Ensemble (final model) |
| Age | 0.3 | 18.2 | 10.2 | 9.6 |
| Sex | 0 | 1.1 | 1.2 | 0.8 |
| Tumour site | 9.4 | 2.6 | 4.8 | 5.6 |
| Response to neoadjuvant therapy | 0 | 0 | 0 | 0 |
| ypT category | 11.2 | 9.2 | 7.4 | 9.2 |
| No. of positive LNs | 3.6 | 30.8 | 40.9 | 25.7 |
| Total no. of LNs examined | 0.4 | 16.7 | 7.0 | 8.0 |
| Lymphovascular invasion | 26.8 | 10.5 | 13.6 | 16.9 |
| Completeness of resection (R0/R1) | 15.9 | 5.2 | 6.1 | 8.9 |
| Tumour grade | 7.0 | 3.2 | 2.1 | 4.0 |
| Neoadjuvant treatment (NACT/NACRT) | 25.4 | 2.5 | 6.8 | 11.4 |

LN, lymph node; NACT, neoadjuvant chemotherapy; NACRT, neoadjuvant chemoradiotherapy.

Models were trained using the `caret`³⁰ and `caretEnsemble`³¹ packages. Individual variable importance was calculated using `iml`³². All are available at <https://CRAN.R-project.org/>. The full R code to train the models is available in *Appendix S2* (supporting information), along with a list of packages used.

The calibrated final model was designed using R Shiny³³ (available freely at <https://uoscancer.shinyapps.io/EROC/>). No data entered into the model were collected or stored.

Results

A total of 812 patients from seven centres were included in model training (*Fig. 1*). Median age was 64 years and most patients were men (84.6 per cent). The majority of tumours were at the GOJ (55.5 per cent), and there were

high proportions of locally advanced tumours (66.7 per cent ypT3–4) and node-positive disease (61.0 per cent). First recurrence of cancer within 1 year of surgery was identified in 236 patients (29.1 per cent). Patients in the early recurrence group were significantly less likely to have responded to neoadjuvant treatment (8.5 *versus* 21.7 per cent), had worse ypT and ypN categories, R1 resection rate and grade of differentiation, and were more likely to have lymphovascular invasion (all $P < 0.001$) (*Table 1*). Clinicopathological data are summarized by centre and type of adjuvant therapy in *Tables S1* and *S2* respectively (supporting information).

Model performance: discrimination

Discrimination was assessed in the training set, internally (via bootstrapping) and internally–externally (across

Table 4 Examples of patients at low, medium and high risk of early recurrence

| | AJCC stage | Description |
|-------------|------------------------|--|
| Low risk | Stage I: ypT0 N0 M0 | A 50-year-old man with a GOJ adenocarcinoma who undergoes neoadjuvant chemoradiotherapy. Postoperative pathology shows ypT0 tumour (responder) with no lymphovascular invasion, R0 resection and a well differentiated tumour. None of 30 lymph nodes sampled is positive. |
| Medium risk | Stage II: ypT3 N0 M0 | A 66-year-old man with an oesophageal adenocarcinoma who undergoes neoadjuvant chemoradiotherapy. Postoperative pathology shows ypT3 tumour (non-responder), lymphovascular invasion, R0 resection and a moderately differentiated tumour. None of 30 lymph nodes sampled is positive. |
| High risk | Stage IIIb: ypT3 N2 M0 | A 70-year-old woman with an oesophageal adenocarcinoma who undergoes neoadjuvant chemotherapy. Postoperative pathology shows ypT3 tumour (non-responder), lymphovascular invasion, R1 resection and poor differentiation. Five of 30 lymph nodes sampled are positive. |

GOJ, gastro-oesophageal junction.

centres). All models demonstrated excellent discrimination on the training set (apparent discrimination). The RF model performed the best (AUC 0.980), followed by the ensemble model (0.902), XGB (0.849) and ELR (0.805) (Table 2). On internal validation, the ensemble model had the best performance (AUC 0.805) and the ELR the worst (0.791) (Fig. 2). Individual centre internal-external validation ROC curves are available in Fig. S3 (supporting information).

Model performance: calibration

Calibration on the training set was visually best in the ELR, and worst in the RF and ensemble models (Fig. S1, supporting information). This was corroborated by the Hosmer–Lemeshow test ($P = 0.806$ for ELR, $P < 0.001$ for RF, $P = 0.030$ for XGB, $P < 0.001$ for ensemble). Probabilities generated by the final model were scaled using isotonic regression. Calibration before and after scaling is shown in Fig. 3. A calibration table can be found in Table S3 (supporting information). The Hosmer–Lemeshow test gave a χ^2 value of 38.0 ($P < 0.001$) before and 4.5 ($P = 0.806$) after scaling. Similarly, the Brier score, a measure of overall model performance, also improved from 0.119 to 0.114.

Variable importance

Coefficients and odds ratios cannot be generated for these models. Therefore, variable importance as a percentage contribution to the model was computed (Table 3). Overall, the most influential predictor variable was number of positive lymph nodes (25.7 per cent), followed by lymphovascular invasion (16.9 per cent). There was considerable variability in importance across models. For example, age contributed 0.3 per cent to the ELR model, 18.2 per cent to the RF model, 10.2 per cent to the XGB model and 9.6 per cent to the final model.

Table 5 Patient examples using final model

| | % | | |
|------------------------------------|----------|-------------|-----------|
| | Low risk | Medium risk | High risk |
| Baseline prediction | 27.4 | 27.4 | 27.4 |
| Age | -0.8 | -0.1 | +4.3 |
| Sex | -0.1 | -0.4 | -2.0 |
| Tumour site | -1.4 | +9.8 | +8.1 |
| Response to neoadjuvant therapy | -0.5 | +0.4 | +0.1 |
| ypT category | -6.5 | +4.9 | +3.2 |
| No. of positive LNs | -10.0 | -32.2 | +9.7 |
| Total no. of LNs examined | -1.2 | -1.9 | -3.1 |
| Lymphovascular invasion | -7.1 | +21.1 | +14.7 |
| Completeness of resection (R0/R1) | -2.3 | -6.0 | +6.1 |
| Tumour grade | -3.0 | -6.9 | +3.6 |
| Neoadjuvant treatment (NACT/NACRT) | +5.8 | +22.2 | -3.9 |
| Final prediction | 0.3 | 38.3 | 68.2 |

The percentage contribution of each variable in each example patient is shown. This is represented as an absolute percentage change from the mean predicted value of 27.4 per cent. A calculator for this is packaged with the online model. LN, lymph node; NACT, neoadjuvant chemotherapy; NACRT, neoadjuvant chemoradiotherapy.

It is important to restate that relationships between the variables and outcome are non-linear and their importance varies considerably according to other variables owing to higher-order interactions. As an example, even though lymph node status was found to be the most influential marker overall, combinations of other variables would make other variables most important in individual patients. To illustrate this and demonstrate how variables interact, three example patients were considered (Tables 4 and 5). The technique used measures the change in prediction from the mean prediction (27.4 per cent) that can be attributed to each predictor variable. This approach (calculation of Shapley value) originates from cooperative game theory.

Discussion

An easy-to-use and robust clinical model for predicting the risk of early recurrence after surgery for oesophageal adenocarcinoma was derived in this study. It uses routinely collected clinical and pathological data that should be available for every patient; together, these allow considerably more precision in risk estimation than would be possible using individual variables that are known to be influential, such as pathological lymph node involvement. The final model demonstrated excellent discrimination, and validation techniques supported the generalizability of the approach.

In addition to prognostication, this model may be useful for planning adjuvant therapy. Early recurrence after oesophagectomy, often before recovery from surgery is complete, is a devastating outcome for patients. Targeting existing and emerging treatment combinations in this patient group to prolong time to recurrence or prevent recurrence is vital, but can only happen with accurate predictions of the likelihood of relapse. The starting point for consideration of treatment escalation or novel combinations (such as immunotherapy) after surgery is the identification of patients who are at high risk of recurrence. The authors have purposefully avoided dichotomization/stratification based on outcome, and presented raw probability in preference to this. This will allow full discussions between surgeons/oncologists and patients regarding the benefits of adjuvant therapy and tailored to the individual patient's postoperative recovery and wishes. It may also allow stratification of adjuvant trials based on layered levels of risk.

This cohort exhibited an early recurrence rate of 29.1 per cent, which is similar to that in previous reports^{3–5,8} where this outcome was specified explicitly. There was also an R1 resection rate of 28.4 per cent, in line with previously reported data^{34,35} based on an RCP definition of CRM positivity (CRM less than 1 mm is positive). In univariable analysis, all factors expected to correlate with worse prognosis (including ypT, ypN, lymphovascular invasion, R1 resection and grade of differentiation) were significantly worse in patients who developed early recurrence. This validates the present cohort as a true representation of contemporary practice and a sensible place to begin building more complex models.

Discrimination of the different models was similar, with minimal variability in AUC values between models on validation. However, the ensemble model consistently performed the best and is a suitable choice for the final model. The decline in performance from the training set to validation, which was particularly marked for the RF and ensemble models, is a consequence of the tuning process,

whereby the optimum values are chosen from a grid of thousands after repeated tests (in this case repeated 10-fold cross-validation). In this setting, the apparent performance of the model on the training set is overestimated and should be disregarded.

There was marked heterogeneity in variable importance between models. This is interesting, particularly in the context of the models performing so similarly overall, and supports the idea of combining them to capture different patient information. The most important variables overall were number of positive lymph nodes and lymphovascular invasion, which accounted for 42.6 per cent of performance in the final model. This is not only biologically sensible, but the subject of several recent publications^{12,36,37} and ongoing translational work. Although not available for this study, more detail regarding lymphadenopathy, such as downstaging and anatomical location, would probably be informative. It is difficult to reach firm conclusions regarding variables considering the nature of the study. However, the authors draw attention to two facets of the model. First, TRG was the least influential variable across the board, with an importance of almost 0 per cent. This suggests that in itself TRG adds no information over the other measured variables in predicting early outcomes. This is in keeping with emerging data regarding the genomic disparity between primary tumours and their metastasis (lymph node or distant)³⁸, and a previous report¹² of the importance of lymph node downstaging to clinical outcome. Second, type of treatment was the third most important determinant of outcome, with NACT having an advantage over NACRT. In this cohort, although the postoperative pathology was considerably more favourable after NACRT, the rate of early recurrence was no less, and tended to be higher (NACRT 35.5 per cent, NACT 27.5 per cent; $P=0.061$ (Table S2, supporting information)). This suggests that, although postoperative pathology is more favourable with NACRT, this does not translate to better outcome^{39–41}; hence ypT3 N1 R0 status after NACT does not have the same meaning as a ypT3 N1 R0 result after NACRT, at least in the early phase after treatment. This is important in postoperative discussions with patients. As the machine learning approaches detailed here allow interactions between variables, the model suggests that NACRT confers a greater risk; however, this increased risk is conditional on the other variables being static rather than an overall increase in risk from having NACRT.

To explore this further, details of recurrence location (locoregional *versus* distant) would be informative. However, owing to the historical nature of the data for the majority of the patients (collected for the first study) it was not possible to ascertain this reliably for most of the cohort.

The concern with NACRT is that improved locoregional control is at the expense of undertreatment of microscopic distant disease, particularly where the radiotherapy field is limited anatomically (for example with GOJ tumours). The expected consequence of this would be fewer locoregional recurrences and more distant recurrences, although this has not been demonstrated in other comparative studies and a recently published RCT⁴¹.

The present study lacks the number of patients needed to separately analyse the influence of neoadjuvant treatment on oesophageal and GOJ tumours, however, the individual variable importance calculation available in the web app allows some insight to be gained. Here, the relative negative influence of NACRT (increased risk of recurrence compared with NACT) is, on the whole, more pronounced for GOJ tumours compared with oesophageal tumours (an example of a second-order interaction), despite the recurrence rate being higher for oesophageal than GOJ tumours.

Other risk factors for early recurrence, including perioperative blood transfusion⁴², complications of surgery⁴³ and preoperative staging, were not available for this study, but are less discriminatory. Nor were precise neoadjuvant regimens available for all patients. It is therefore unclear whether these results would be influenced by completion of treatment as prescribed, or indeed by whether any adjuvant therapy was given. The absence of these factors seems to have minimal effect on the model, suggesting a small margin of effect on outcomes. Combining these factors could potentially increase the performance of the present model if incorporated in the future. Ultimately, differential gene expression and mutation^{44,45} may well determine prognostication and treatment pathways⁴⁶, but such data are unlikely to be available universally for some years. Until then, clinical and histopathological data remain the standard.

In that context, gains from mathematical and computer-based techniques are key to precision in delivery of cancer care. Here, several modern approaches that produce viable models were demonstrated. This study used a data set that was relatively small and simple in a machine learning context, and the improvement in performance over a standard logistic regression was small (internal validation AUC 0.781). This is nonetheless important as such an improvement is in effect 'free'. The strengths of this study lie in its multicentre nature and the heterogeneity of the cohort. This approach should maximize the utility of the model on external populations. All the data points used should be collected routinely at the majority of institutions, which should allow uptake without change in practice. The College of American Pathologists (CAP) definition of CRM positivity (CRM

positive if there is tumour at the resection margin) was derivable for centre G, and performance was preserved in this subgroup if that definition was used instead of the RCP definition (AUC 0.813 with model generated on centres A–F (650 patients) and validated on centre G (162)) (Fig. S2, supporting information), supporting utility in both settings. The study focused on predictive model study design and reporting as suggested by the AJCC⁴⁷ and TRIPOD⁴⁸ statements.

The training set was limited to patients undergoing neoadjuvant therapy for adenocarcinoma of the oesophagus. No attempt was made to apply the model to a chemotherapy-naïve population, and it is unlikely to calibrate well in this group owing to the differing influence on survival of yp compared with p staging⁴⁹. It is also unclear whether the model would be valid in patients with squamous cell carcinoma; the authors advocate an early external validation exercise using this patient group. A formal prospective validation/recalibration using the CAP definition of CRM positivity would also be beneficial. Simulation studies have suggested that 100–200 cases (positives) are required for accurate validation⁵⁰, which, assuming a stable incidence, would require approximately 380–760 patients. A further limitation was the significant proportion of the original patients with missing data, which will have introduced a degree of selection bias. Multiple imputation is possible as a means of addressing this, but was considered less appropriate in this study because of the high proportion of missing data for the outcome measure and the lack of an external validation set.

A large multicentre cohort of patients who underwent oesophagectomy has been used to derive an accurate prediction model for early cancer recurrence, with excellent performance on validation. Machine learning techniques represent an attractive proposition for maximizing performance of predictive models.

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References

- 1 Maynard N, Chadwick G, Varaganam M, Brand C, Cromwell D, Riley S *et al*. National Oesophago-Gastric Cancer Audit 2017. *R Coll Surg Engl* 2017: 103.

- 2 Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002; **359**: 1727–1733.
- 3 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M *et al.*; MAGIC Trial Participants. Perioperative chemotherapy *versus* surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11–20.
- 4 Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI *et al.*; CROSS study group. 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**: 1090–1098.
- 5 Davies AR, Pillai A, Sinha P, Sandhu H, Adeniran A, Mattsson F *et al.* Factors associated with early recurrence and death after esophagectomy for cancer. *J Surg Oncol* 2014; **109**: 459–464.
- 6 Low DE, Kuppusamy MK, Alderson D, Cecconello I, Chang AC, Darling G *et al.* Benchmarking complications associated with esophagectomy. *Ann Surg* 2019; **269**: 291–298.
- 7 Shapiro J, Biermann K, van Klaveren D, Offerhaus GJ, Ten Kate FJ, Meijer SL *et al.* Prognostic value of pretreatment pathological tumor extent in patients treated with neoadjuvant chemoradiotherapy plus surgery for esophageal or junctional cancer. *Ann Surg* 2017; **265**: 356–362.
- 8 Goense L, van Rossum PSN, Xi M, Maru DM, Carter BW, Meijer GJ *et al.* Preoperative nomogram to risk stratify patients for the benefit of trimodality therapy in esophageal adenocarcinoma. *Ann Surg Oncol* 2018; **25**: 1598–1607.
- 9 Caruana R. An empirical comparison of supervised learning algorithms. *Proceedings of the 23rd International Conference on Machine Learning*, Pittsburgh, 2006.
- 10 Fernández-Delgado M, Cernadas E, Barro S, Amorim D. Do we need hundreds of classifiers to solve real world classification problems? *J Mach Learn Res* 2014; **15**: 3133–3181.
- 11 Christodoulou E, Ma J, Collins GS, Steyerberg EW, Verbakel JY, van Calster B. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J Clin Epidemiol* 2019; **110**: 12–22.
- 12 Noble F, Lloyd MA, Turkington R, Griffiths E, O'Donovan M, O'Neill JR *et al.*; OCCAMS consortium. Multicentre cohort study to define and validate pathological assessment of response to neoadjuvant therapy in oesophagogastric adenocarcinoma. *Br J Surg* 2017; **104**: 1816–1828.
- 13 Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF *et al.* Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994; **73**: 2680–2686.
- 14 Stiles BM, Salzler GG, Nasar A, Paul S, Lee PC, Port JL *et al.* Clinical predictors of early cancer-related mortality following neoadjuvant therapy and oesophagectomy. *Eur J Cardiothorac Surg* 2015; **48**: 455–460.
- 15 Grabsch HI, Mapstone NP, Novelli M. *Standards and datasets for reporting cancers. Dataset for the histopathological reporting of oesophageal carcinoma (2nd edition)*; 2019. <https://www.rcpath.org/uploads/assets/f8b1ea3d-5529-4f85-984c8d4d8556e0b7/g006-dataset-for-histopathological-reporting-of-oesophageal-and-gastric-carcinoma.pdf> [accessed 4 December 2019].
- 16 Zou H, Hastie T. Regularization and variable selection via the elastic net. *J R Stat Soc Series B Stat Methodology* 2005; **67**: 301–320.
- 17 Breiman L. Random forests. *Mach Learn* 2001; **45**: 5–32.
- 18 Chen T, Guestrin C. XGBoost: a scalable tree boosting system. *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining: KDD 2016, San Francisco*, 2016; 785–794.
- 19 Pavlou M, Ambler G, Seaman SR, Guttman O, Elliott P, King M *et al.* How to develop a more accurate risk prediction model when there are few events. *BMJ* 2015; **351**: h3868.
- 20 Ranstam J, Cook JA. LASSO regression. *Br J Surg* 2018; **105**: 1348–1348.
- 21 Caruana R, Niculescu-Mizil A, Crew G, Ksikes A. Ensemble selection from libraries of models. *Proceedings of the 21st International Conference on Machine Learning*, Banff, 2004.
- 22 Steyerberg EW, Harrell FE Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis *J Clin Epidemiol* 2001; **54**: 774–781.
- 23 Steyerberg EW, Moons KG, van der Windt DA, Hayden JA, Perel P, Schroter S *et al.*; PROGRESS Group. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 2013; **10**: e1001381.
- 24 Harrell F. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis* (2nd edn). Springer: New York, 2015.
- 25 Steyerberg EW, Harrell FE Jr. Prediction models need appropriate internal, internal–external, and external validation. *J Clin Epidemiol* 2016; **69**: 245–247.
- 26 Niculescu-Mizil A, Caruana R. Predicting good probabilities with supervised learning. *Proceeding of the 22nd International Conference on Machine Learning*, Bonn, 2005; 625–632.
- 27 Chen W, Sahiner B, Samuelson F, Pezeshk A, Petrick N. Calibration of medical diagnostic classifier scores to the probability of disease. *Stat Methods Med Res* 2018; **27**: 1394–1409.
- 28 Lundberg S, Lee SI. A unified approach to interpreting model predictions. *Proceedings of the 31st International Conference on Neural Information Processing Systems*, Long Beach, California, 2017; 4768–4777.
- 29 Nanayakkara S, Fogarty S, Tremeer M, Ross K, Richards B, Bergmeir C *et al.* Characterising risk of in-hospital mortality following cardiac arrest using machine learning: a retrospective international registry study. *PLoS Med* 2018; **15**: e1002709.

- 30 Kuhn M. *caret: Classification and Regression Training (Ver 6.0-81)*. 2018. <https://cran.r-project.org/package=caret> [accessed 4 December 2019].
- 31 Deane-Mayer Z, Knowles J. *CaretEnsemble: Ensembles of Caret Models (ver 2.0.0)*. 2016. <https://cran.r-project.org/package=caretEnsemble> [accessed 4 December 2019].
- 32 Molnar C, Bischl B, Casalicchio G. iml: An R Package for interpretable machine learning. *J Open Source Softw* 2018; **3**: 786.
- 33 Chang W, Cheng J, Xie Y, McPherson J. *Shiny: Web Application Framework for R (ver 1.2.0)*. <https://cran.r-project.org/package=shiny> [accessed 4 December 2019].
- 34 Reid TD, Chan DS, Roberts SA, Crosby TD, Williams GT, Lewis WG. Prognostic significance of circumferential resection margin involvement following oesophagectomy for cancer and the predictive role of endoluminal ultrasonography. *Br J Cancer* 2012; **107**: 1925–1931.
- 35 Knight WRC, Zylstra J, Wulaningsih W, Van Hemelrijck M, Landau D, Maisey N *et al.*; Guy's and St Thomas' Oesophago-Gastric Research Group. Impact of incremental circumferential resection margin distance on overall survival and recurrence in oesophageal adenocarcinoma. *BJS Open* 2018; **2**: 229–237.
- 36 Smyth EC, Fassan M, Cunningham D, Allum WH, Okines AF, Lampis A *et al.* Effect of pathologic tumor response and nodal status on survival in the Medical Research Council adjuvant gastric infusional chemotherapy trial. *J Clin Oncol* 2016; **34**: 2721–2727.
- 37 Davies AR, Myoteri D, Zylstra J, Baker CR, Wulaningsih W, Van Hemelrijck M *et al.*; Guy's and St Thomas' Oesophago-Gastric Research Group and PROGRESS Study Group. Lymph node regression and survival following neoadjuvant chemotherapy in oesophageal adenocarcinoma. *Br J Surg* 2018; **105**: 1639–1649.
- 38 Noorani A, Goddard M, Crawte J, Alexandrov LB, Li X, Secrier M *et al.* Genomic evidence supports a clonal diaspora model for metastases of esophageal adenocarcinoma. *bioRxiv* 2018; 454306.
- 39 Klevebro F, Alexandersson von Döbeln G, Wang N, Johnsen G, Jacobsen AB, Friesland S *et al.* A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. *Ann Oncol* 2016; **27**: 660–667.
- 40 Anderegg MCJ, van der Sluis PC, Ruurda JP, Gisbertz SS, Hulshof MCCM, van Vulpel M *et al.* Preoperative chemoradiotherapy versus perioperative chemotherapy for patients with resectable esophageal or gastroesophageal junction adenocarcinoma. *Ann Surg Oncol* 2017; **24**: 2282–2290.
- 41 von Döbeln GA, Klevebro F, Jacobsen AB, Johannessen HO, Nielsen NH, Johnsen G *et al.* Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastroesophageal junction: long-term results of a randomized clinical trial. *Dis Esophagus* 2019; **32**: 1–11.
- 42 Dresner SM, Lamb PJ, Shenfine J, Hayes N, Griffin SM. Prognostic significance of peri-operative blood transfusion following radical resection for oesophageal carcinoma. *Eur J Surg Oncol* 2000; **26**: 492–497.
- 43 Booka E, Takeuchi H, Suda K, Fukuda K, Nakamura R, Wada N *et al.* Meta-analysis of the impact of postoperative complications on survival after oesophagectomy for cancer. *BJS Open* 2018; **2**: 276–284.
- 44 Ueda M, Iguchi T, Masuda T, Nakahara Y, Hirata H, Uchi R *et al.* Somatic mutations in plasma cell-free DNA are diagnostic markers for esophageal squamous cell carcinoma recurrence. *Oncotarget* 2016; **7**: 62 280–62 291.
- 45 Lv H, He Z, Wang H, Du T, Pang Z. Differential expression of miR-21 and miR-75 in esophageal carcinoma patients and its clinical implication. *Am J Transl Res* 2016; **8**: 3288–3298.
- 46 Walker RC, Underwood TJ. Molecular pathways in the development and treatment of oesophageal cancer. *Best Pract Res Clin Gastroenterol* 2018; **36–37**: 9–15.
- 47 Kattan MW, Hess KR, Amin MB, Lu Y, Moons KG, Gershenwald JE *et al.* American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. *CA Cancer J Clin* 2016; **66**: 370–374.
- 48 Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. *BMJ* 2015; **350**: g7594.
- 49 Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann Cardiothorac Surg* 2017; **6**: 119–130.
- 50 Collins GS, Ogundimu EO, Altman DG. Sample size considerations for the external validation of a multivariable prognostic model: a resampling study. *Stat Med* 2016; **35**: 214–226.

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.