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Original Article

Severe lymphopenia acquired during chemoradiotherapy for esophageal cancer: Incidence and external validation of a prediction model

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ABSTRACT

Background: The incidence of grade 4 lymphopenia in patients treated with chemoradiotherapy (CRT) according to Chemoradiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) regimen is unclear. The primary aim was to determine the incidence of grade 4 lymphopenia during CROSS for esophageal cancer. Secondary aims were to externally validate a prediction model for grade 4 lymphopenia and compare overall survival between patients with and without grade 4 lymphopenia.

Methods: Patients who underwent CRT for esophageal cancer between 2014 and 2019 were eligible for inclusion. Patients with a planned radiation dose of 41.4 Gy (CROSS) or 50.4 Gy (“extended-CROSS”) and concurrent carboplatin and paclitaxel were included. The primary outcome was the incidence of grade 4 lymphopenia during CRT defined according to Common Terminology Criteria for Adverse Events version 5.0 (i.e. lymphocyte count nadir < 0.2 μL). The secondary outcome measures were the prediction model’s external performance (i.e. discrimination and calibration). Overall survival for patients with versus without grade 4 lymphopenia was compared using Kaplan–Meier analysis.

Results: A total of 219 patients were included of whom 176 patients (80%) underwent CROSS and 43 patients (20%) extended-CROSS. The incidence of grade 4 lymphopenia was 11% in CROSS and 33% in extended-CROSS ($p < 0.001$). External discrimination yielded a c-statistic of 0.80 (95% confidence interval: 0.70–0.89). External calibration of the model was poor in CROSS but fair in extended-CROSS. Adjusted calibration using intercept correction (adjusted for the lower a-priori risk for grade 4 lymphopenia in CROSS) showed fair agreement between the observed and predicted risk for grade 4 lymphopenia. Median overall survival in patients with versus without grade 4 lymphopenia was 12.7 versus 42.5 months ($p = 0.045$).

Conclusion: The incidence of grade 4 lymphopenia is significantly higher in esophageal cancer patients receiving extended-CROSS compared to those receiving CROSS. The prediction model demonstrated good external performance in the setting of the CROSS-regimen and could be used to identify patients at high-risk for grade 4 lymphopenia who might be eligible for lymphopenia–mitigating strategies.

Neoadjuvant or definitive chemoradiotherapy (CRT) is a standard curative treatment approach for locally-advanced esophageal cancer [1–3]. A common neoadjuvant or definitive CRT regimen in Europe is Chemoradiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) consisting of carboplatin and paclitaxel chemotherapy with a concurrent radiation dose of 41.4 Gy (CROSS) or 50.4 Gy (“extended-CROSS”) [1]. Lymphopenia is considered an adverse event and the severity of lymphopenia can be graded using the Common Terminology Criteria for Adverse Events (version 5.0). Grade 4 lymphopenia is observed in up to 40% of esophageal cancer patients treated with CRT as lymphocytes are the most radiosensitive hematopoietic cells [4]. Lymphocytes play a vital role in the immune system, including tumor surveillance [5,6]. Accordingly, several recent studies have identified severe radiation-induced lymphopenia as a detrimental prognostic factor associated with worse progression-free and overall survival in many solid tumors, including esophageal cancer [5,7–10].

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The above arguments pose a pressing need for strategies to identify patients at high risk for severe radiation-induced lymphopenia in order to identify patients eligible for potential lymphopenia-mitigating strategies. Thus, a pretreatment prediction model for the development of grade 4 lymphopenia during CRT for esophageal cancer was developed and validated in the MD Anderson Cancer Center and Mayo Clinic, respectively [11]. Grade 4 lymphopenia was observed in 37% and 41% of patients, respectively. A prediction model with satisfactory model performance was developed and validated (c-statistic after internal validation 0.76 and after external validation 0.71). However, the applicability of this model in esophageal cancer patients treated with CRT according to the CROSS or extended-CROSS regimen is unclear because this model was developed in esophageal cancer patients treated with concurrent photon- or proton-based radiotherapy to a dose of 50.4 Gy (rather than 41.4 Gy of the CROSS regimen) and mainly fluoropyrimidine-based chemotherapy (rather than carboplatin and paclitaxel) [2].

The primary aim of this cohort study was to assess the incidence of grade 4 lymphopenia in esophageal cancer patients treated with photon-based CRT according to the CROSS or extended-CROSS regimen. A secondary aim was to externally validate an existing pretreatment prediction model constructed for grade 4 lymphopenia and assess its performance in esophageal cancer patients treated with CRT according to the CROSS or extended-CROSS regimen. Finally, a secondary aim was to compare overall survival between patients with and without grade 4 lymphopenia.

Methods

Study design

This study was approved by the institutional review board of the UMC Utrecht and the need for informed consent was waived. The study was reported according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and the guidelines of the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (Supplementary File A) [12].

Patient inclusion

Consecutive patients with biopsy-proven adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the esophagus who underwent carboplatin and paclitaxel with concurrent photon-based planned radiotherapy to a dose of 41.4 Gy (CROSS) or 50.4 Gy (“extended-CROSS”) at the UMC Utrecht between 2014 and 2019 were eligible for inclusion in this retrospective cohort study. Carboplatin was targeted at an area under the curve of 2 mg per milliliter per minute, paclitaxel at a dose of 50 mg per square meter of body-surface area, and both were administered intravenously [1]. The total radiation dose was given in 23 (CROSS) or 28 (extended-CROSS) fractions of 1.8 Gy, with 5 fractions administered per week, starting on the first day of the first chemotherapy cycle [1]. All patients underwent baseline endoscopy, PET-CT imaging, and external-beam photon-based radiotherapy. Both step-and-shoot intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) were suitable techniques for inclusion. Patients with an incomplete chemotherapy or radiotherapy course (defined as <4 chemotherapy cycles or <23 radiotherapy fractions in case of “CROSS” or <5 chemotherapy cycles or <28 radiotherapy fractions in case of “extended-CROSS”) were excluded. In addition, patients with missing data on predictors from the existing pretreatment prediction model, with <3 lymphocyte measurements during CRT or in whom a second target (e.g. lung) was irradiated were excluded.

Predictors

Predictors for the development of grade 4 lymphopenia of the existing pretreatment prediction model were higher age, larger planning target volume (PTV) in interaction with a lower body mass index (BMI) and lower baseline absolute lymphocyte count. Age and BMI were measured at the start of CRT. Full blood count measurements including absolute lymphocyte counts were extracted at baseline (≤30 days before the start of CRT) and for each week during CRT using the Utrecht Patient Oriented Database (UPOD) at the UMC Utrecht [13]. Age, BMI, and PTV were analyzed as continuous variables [14]. Contouring of the gross tumor volume (GTV) was performed based on the endoscopy and PET-CT imaging results. The clinical target volume (CTV) was defined by extending the GTV by 3 cm in the cranial and caudal direction along the esophageal tract, or by 2 cm in the caudal direction in cases where the CTV extended in the stomach, as well as an extension of 0.5 cm in circumferential direction without violation of the anatomical boundaries of the surrounding organs. The planning target volume (PTV) margin was 1 cm in all directions [15]. The existing pretreatment prediction model logistic regression formula is described as follows [11]:

$$\log\left(\frac{p}{1-p}\right) = -22.845 + 0.021 * \text{Age} + 0.516 * \text{BMI} + 3.579 * \log(PTV) - 0.086 * \text{BMI} * \log(PTV) + 0.949 * \text{IMRT} \quad [0 = \text{no};\ 1 = \text{yes}] - 1.019 * \text{baselineabsolutelymphocytecount}.$$

Outcomes

Grade 4 lymphopenia was defined as an absolute lymphocyte count nadir < 0.2 μL according to the Common Terminology Criteria for Adverse Events version 5.0. The primary outcome measure was the incidence of grade 4 lymphopenia during CRT according to CROSS or extended-CROSS. The secondary outcome measures were the existing prediction model’s performance for predicting grade 4 lymphopenia (i.e. discrimination and calibration) and overall survival between patients with and without grade 4 lymphopenia. The overall survival was defined as the time interval between the start of CRT and death or last follow-up.

Statistical analysis

Comparison between grade 4 and non-grade 4 lymphopenia groups for continuous normally distributed and non-normally distributed variables at baseline was performed using the Student’s T-tests and Mann Whitney U test, respectively. Categorical variables were compared using the Fisher’s exact test. Spearman correlation coefficients among predictors and the outcome were calculated. Complete-case analysis was performed (i.e. patients with missing predictors were excluded). The discriminative performance of the model was assessed using the c-statistic and was illustrated with a receiver operating characteristic (ROC)-curve. Subsequently, sensitivity analyses were performed by separately assessing the discriminative model performance in adenocarcinoma and squamous cell carcinoma patients.

The model calibration was evaluated by comparing the observed risk of grade 4 lymphopenia in patients treated with CROSS or extended-CROSS with 4 equal size predicted risk groups using the existing prediction model. The overall survival was calculated using Kaplan–Meier analysis and compared between groups using the log-rank test. All statistical analyses were performed using R version 3.5.1 (packages ‘foreign’, ‘survival’, ‘rms’ and ‘ggplot2’). A p-value of <0.05 was considered statistically significant.

Results

A total of 393 patients were identified, of whom 86 patients were excluded because of missing baseline absolute lymphocyte measurements, 57 patients because of <3 lymphocyte measurements during CRT, 24 patients because of simultaneous irradiation of a second target, 4 patients with an incomplete radiotherapy course, and 3 patients because of missing baseline BMI measurements. Consequently, 219 patients were included. The patient selection is presented in Fig. 1.

Patients were predominantly male (76%) and were diagnosed with a clinical T3 (73%), N1 (43%) adenocarcinoma (62%) of the lower third of the esophagus (69%). The radiation modality was photon-based in all cases, using VMAT in 77% and step-and-shoot IMRT in 23%. The CRT regimen was in 176 patients (80%) CROSS and in 43 patients (20%) extended-CROSS. Baseline patient characteristics are presented in Table 1.

Grade 4 lymphopenia during CRT was observed in 34 patients (16%). The incidence of grade 4 lymphopenia during CROSS versus extended-CROSS was 11% versus 33%, respectively ($p < 0.001$; Fig. 1). Grade 4 lymphopenia was observed predominantly 5 weeks after the start of CRT. The number of lymphocyte measurements was 4 in 164 patients (75%), 5 in 18 patients (8%), 6 in 34 patients (16%) and 7 in 3 patients (1%). The total number of lymphocyte measurements was 971. The course of lymphocyte counts per week stratified for CRT regimen is presented in Fig. 2.

Patients who developed grade 4 lymphopenia during CRT had a larger PTV ($p < 0.001$), lower baseline absolute lymphocyte count ($p < 0.001$), comparable age ($p = 0.057$) and higher clinical tumor ($p = 0.014$) and nodal stage ($p = 0.024$) as compared with patients who did not develop grade 4 lymphopenia. Supplementary File 2 shows examples of planned radiation dose to GTV, CTV and PTV. Supplementary File 3 shows the correlations between BMI, PTV, clinical tumor and nodal stage, baseline lymphocyte count, and grade 4 lymphopenia. Applying the existing prediction model to this cohort yielded an external discriminatory c-statistic of 0.80 (95% confidence interval: 0.70–0.89). The model discrimination is presented in Fig. 3. Sensitivity analyses for patients with adenocarcinoma versus squamous cell carcinoma histology yielded a discriminatory c-statistic of 0.82 (95% CI: 0.71–0.94) versus 0.77 (95% CI: 0.62–0.93).

Calibration of the existing prediction model in this external cohort was fair in extended-CROSS and poor in CROSS (i.e. consistent overestimation of the predicted risk compared with the observed risk of grade 4 lymphopenia in CROSS). The separate calibration of the existing prediction model in extended-CROSS and CROSS are presented in Supplementary File 4 and Supplementary File 5, respectively. The existing model was updated for CROSS using intercept correction (i.e. from −22.845 to −23.459) to adjust for a lower a-priori risk for grade 4 lymphopenia in CROSS as compared with the cohort used for development and validation. Adjusted calibration showed fair agreement between the observed and predicted risk for grade 4 lymphopenia in CROSS and extended-CROSS. The updated calibration after intercept correction is presented in Fig. 4. The updated pretreatment prediction model logistic regression formula is described as follows:

$$\log\left(\frac{p}{1-p}\right) = -22.845 + 0.021 * \text{Age} + 0.516 * \text{BMI} + 3.579 * \log(PTV) - 0.086 * \text{BMI} * \log(PTV) + 0.949 * \text{IMRT}[0 = \text{no}; 1 = \text{yes}] - 1.019 * \text{baselinea bsolutelymphocytecount} - 0.614 * \text{Numberoffractions}[0 = 28; 1 = 23].$$

The median follow-up time was 26.7 months (range: 1–82 months). Median overall survival in patients with versus without grade 4 lymphopenia was 12.7 months versus 42.5 months ($p = 0.045$). The overall survival stratified for grade 4 lymphopenia is presented in Fig. 5.

Discussion

The incidence of grade 4 lymphopenia in esophageal cancer patients treated with CRT according to extended-CROSS was higher as compared with CROSS (i.e. 33% versus 11%, respectively). External validation of a pretreatment existing prediction model in this cohort yielded a good discriminative performance (c-statistic 0.80). Calibration of the existing model was fair in extended-

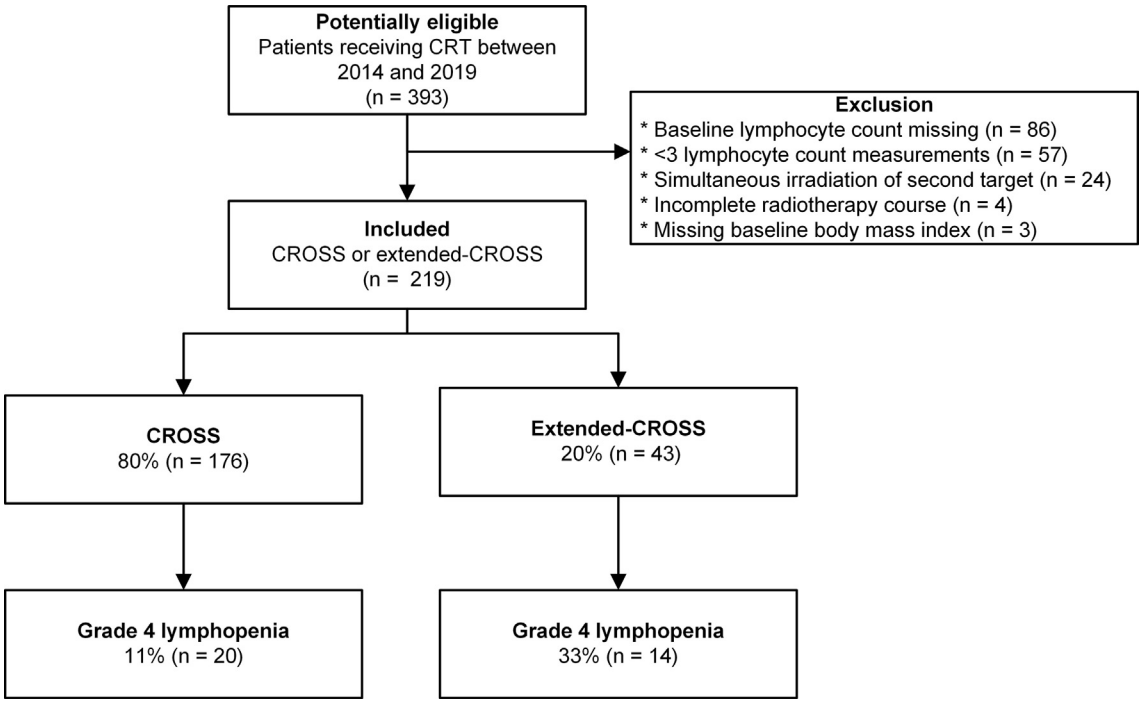

Fig. 1. Patient selection.

Table 1
Patient characteristics.

Stratified by grade 4 lymphopenia (G4L)	No G4L (*n* = 185)	G4L (*n* = 34)	*p*-value
Sex (%)			0.485
Male	144 (77.8)	24 (70.6)	
Female	41 (22.2)	10 (29.4)	
Year start CRT(%)			0.108
2014	29 (15.7)	8 (23.5)	
2015	39 (21.1)	4 (11.8)	
2016	43 (23.2)	6 (17.6)	
2017	35 (18.9)	12 (35.3)	
2018	39 (21.1)	4 (11.8)	
Median body mass index [IQR]	24.5 [22.1, 27.1]	25.5 [21.5, 27.5]	0.411
Median age [IQR]	67.0 [60.0, 72.0]	68.0 [64.3, 73.0]	0.057
Tumor location (%)			0.393
Cervical esophagus	4 (2.2)	0 (0.0)	
Upper third of esophagus	15 (8.1)	1 (2.9)	
Middle third of esophagus	37 (20.0)	10 (29.4)	
Lower third of esophagus	129 (69.7)	23 (67.6)	
Clinical T-stage (%)			0.014
1	3 (1.6)	0 (0.0)	
2	29 (15.7)	0 (0.0)	
3	134 (72.4)	25 (73.5)	
4a	4 (2.2)	1 (2.9)	
4b	15 (8.1)	8 (23.5)	
Clinical N-stage (%)			0.024
0	67 (36.2)	5 (14.7)	
1	80 (43.2)	15 (44.1)	
2	34 (18.4)	12 (35.3)	
3	4 (2.2)	2 (5.9)	
Histology (%)			0.545
Adenocarcinoma	115 (62.2)	19 (55.9)	
Adenosquamous carcinoma	3 (1.6)	0 (0.0)	
Squamous cell carcinoma	67 (36.2)	15 (44.1)	
Radiotherapy regimen (%)			0.018
CROSS	156 (84.2)	20 (58.8)	
extended-CROSS	29 (15.7)	14 (41.2)	
Radiation technique (%)			0.743
Intensity-modulated radiotherapy	41 (22.2)	9 (26.5)	
Volumetric arc therapy	144 (77.8)	25 (73.5)	
Median planning target volume [IQR]*	433 [343, 575]	661 [455, 853]	<0.001
Median baseline neutrophil count [IQR] †	5.26 [4.28, 6.76]	5.59 [4.69, 6.53]	0.385
Median baseline lymphocyte count [IQR] †	1.92 [1.58, 2.25]	1.30 [1.07, 1.85]	<0.001
Median baseline neutrophil-to-lymphocyte ratio [IQR]	2.75 [2.18, 3.69]	4.22 [3.06, 5.84]	<0.001
Median baseline haemoglobin [IQR] ‡	8.97 [8.30, 9.50]	8.69 [8.11, 9.46]	0.221
Median baseline platelet count [IQR] †	256 [217, 298]	259 [215, 355]	0.400

* = volume in mL; † = 10^3/mL; ‡ = mmol/L.

CROSS and poor in CROSS (i.e. consistent overestimation of the predicted risk as compared with the observed risk of grade 4 lymphopenia in CROSS). The model was updated for CROSS using intercept correction. The model was adjusted for a lower incidence of grade 4 lymphopenia in CROSS (11%) as compared with the cohorts used for development (37%) and validation (40%) [11]. This difference in the proportion of grade 4 lymphopenia in CROSS could be explained by a lower planned radiation dose and/or lower number of fractions in CROSS (41.4 Gy and 23 fractions) as compared with the cohort used for development (50.4 Gy and 28 fractions) and validation (50.4 Gy and 28 fractions in 87% of patients) [11]. Accordingly, the proportion of grade 4 lymphopenia in extended-CROSS (33%) was comparable with cohorts used for development (37%) and validation (40%).

This model is predominantly applicable to patients in Western countries because the majority of the patients included in the study were diagnosed with an adenocarcinoma. However, sensitivity analyses demonstrated that the model discrimination for patients with adenocarcinoma was comparable to patients with squamous cell carcinoma (c-index: 0.82 versus 0.77, respectively). This suggests that the model could also apply to Asian countries. The prediction model allows for the identification of individual patients at high risk for radiation-induced severe lymphopenia before treatment. These patients might be eligible for potential lymphopenia-mitigating strategies, such as sparing lymphocyte-rich organs-at-risk in radiotherapy planning or reducing integral body radiation dose using proton-based radiotherapy instead of photons [16–17]. In addition, margin reduction through modern adaptive radiotherapy (e.g. MR Linac) could be beneficial to the lymphocyte count since PTV is highly predictive of lymphopenia [18–20].

Chemotherapy could also contribute to lymphopenia by inducing bone marrow suppression [21]. This study could not determine the effect of chemotherapy on lymphopenia because all patients were treated with CROSS chemotherapy (i.e. carboplatin and paclitaxel). However, the impact of chemotherapy on the lymphocyte count appears to be limited as lymphopenia is also observed in patients treated with radiotherapy alone (i.e. without concurrent chemotherapy) [22–23]. Moreover, in the esophageal cancer cohort used for model development, grade 4 lymphopenia was not associated with previous induction chemotherapy nor the type of concurrent chemotherapy (e.g. taxane and 5-FU versus platinum and 5-FU or taxane and platinum or other) [11].

The prognostic importance of lymphopenia was demonstrated by a significant and clinically relevant worse overall survival of

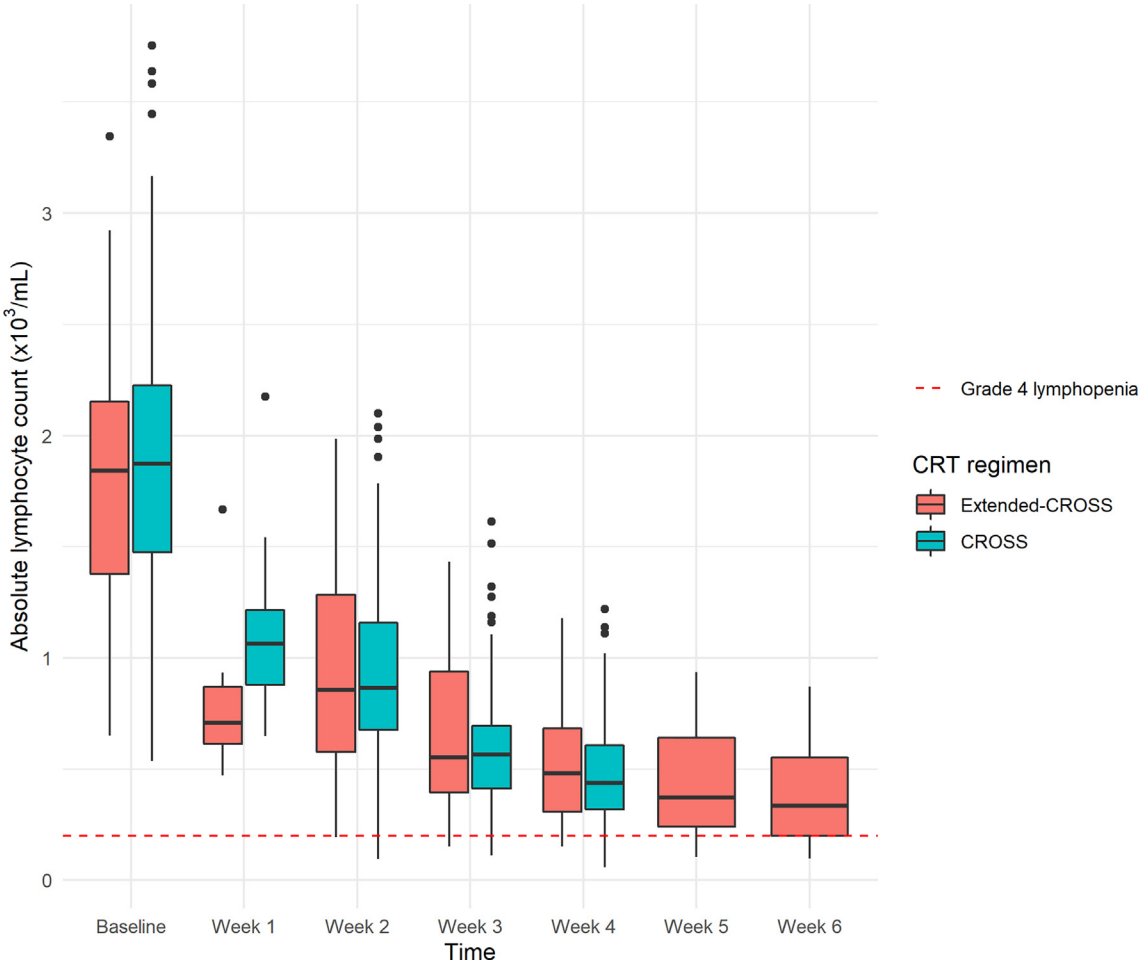

Fig. 2. Course of lymphocyte counts per week stratified for chemoradiotherapy regimen.

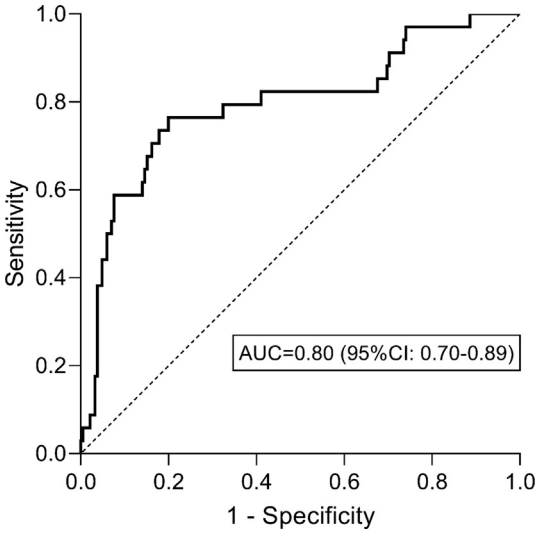

Fig. 3. Model discrimination.

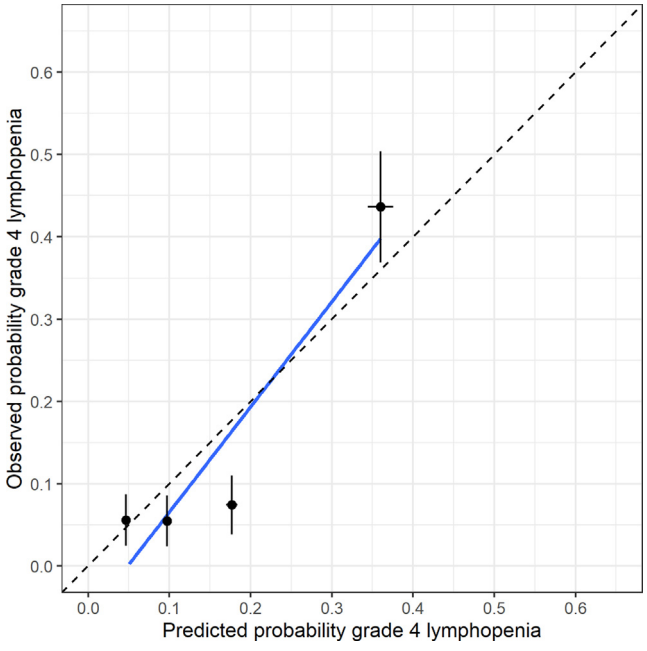

Fig. 4. Model calibration after intercept correction.

patients with grade 4 lymphopenia as compared with those without grade 4 lymphopenia (12.7 months as compared with

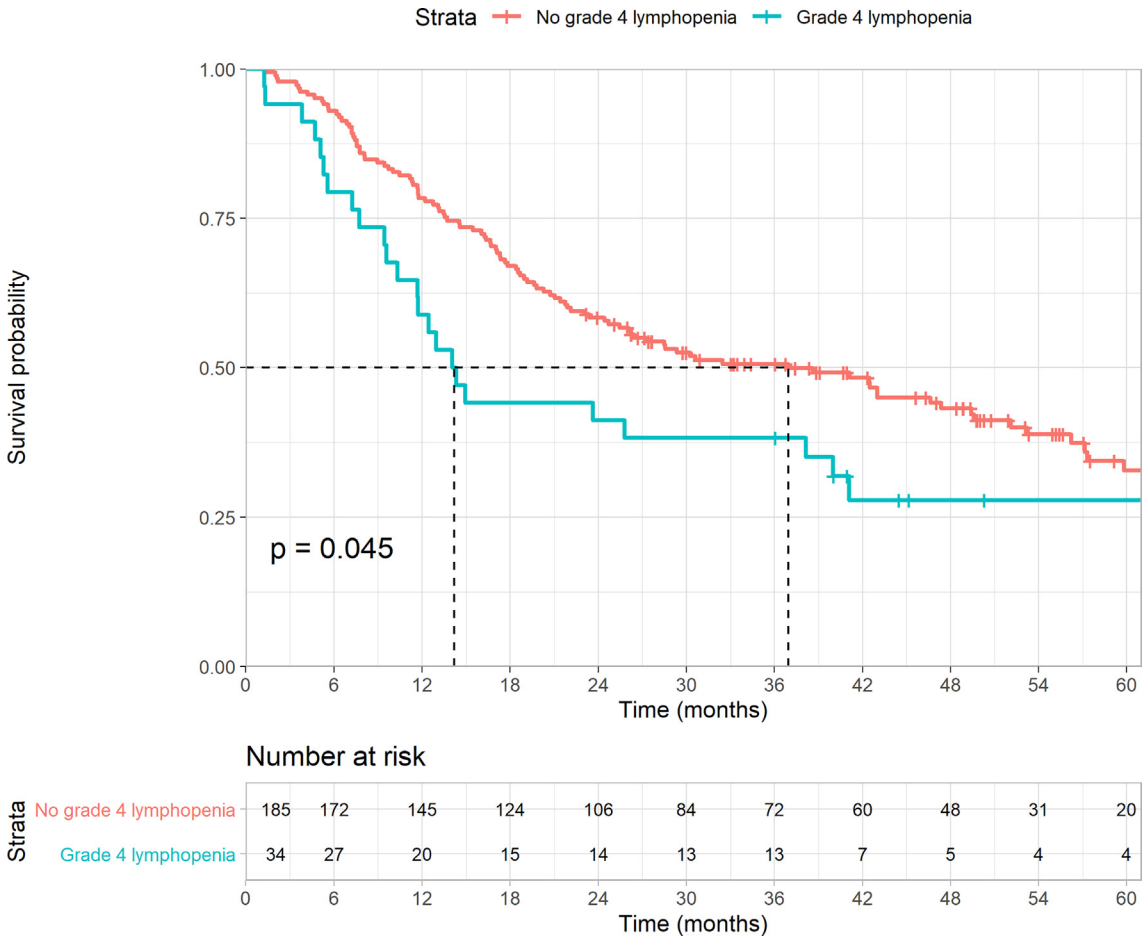

Fig. 5. Overall survival stratified for grade 4 lymphopenia.

42.5 months). The causality of this relationship cannot be inferred from the results of this study. However, several studies have demonstrated an independent association between grade 4 lymphopenia acquired during CRT and reduced overall survival in esophageal cancer [24,25].

Certain limitations apply to this study. First, this study could not address a causal relationship between grade 4 lymphopenia and overall survival. Second, the exclusion of some patients may have introduced a diminished precision of estimations. This exclusion was predominantly the result of the hospital of diagnosis because lymphocyte measurements could not be extracted from peripheral hospitals which referred patients for radiotherapy/-surgery only. As the hospital of diagnosis is mainly the hospital which is nearest to the patient, we believe this did not result in a clinically relevant selection bias. Finally, besides sensitivity analyses for adenocarcinoma and squamous cell carcinoma patients, this study was not able to formally address the applicability of this model in Asian patients. Furthermore, this study is strengthened by the homogenous study cohort. In this study, patients who underwent CRT according to the CROSS or extended-CROSS regimen were included, which is the current standard of care in many European countries. Therefore, this study has excellent generalizability.

In conclusion, the incidence of grade 4 lymphopenia is significantly higher in esophageal cancer patients receiving extended-CROSS (i.e. 50.4 Gy) compared to those receiving CROSS (i.e. 41.4 Gy). External validation of an existing pretreatment prediction model yielded good discriminative performance (c-statistic 0.80). Calibration of the existing model was fair in extended-CROSS and in CROSS patients (after intercept correction). As such, the model allows for pretreatment identification of individual patients at high risk for radiation-induced lymphopenia who might be eligible for lymphopenia-mitigating strategies.

Funding

Not applicable.

Conflict of interest

No conflict of interest relevant for this work.

Data sharing agreement

All data generated and analyzed during this study are included in this published article (and its supplementary information files).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.08.009.

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