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ORIGINAL ARTICLE

Improving survival prediction of oesophageal cancer patients treated with external beam radiotherapy for dysphagia

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ABSTRACT

Introduction: The recent POLDER trial investigated the effects of external beam radiotherapy (EBRT) on dysphagia caused by incurable oesophageal cancer. An estimated life expectancy of minimally three months was required for inclusion. However, nearly one-third of the included patients died within three months. The aim of this study was to investigate if the use of prediction models could have improved the physician's estimation of the patient's survival.

Methods: Data from the POLDER trial ($N = 110$) were linked to the Netherlands Cancer Registry to retrieve patient, tumour, and treatment characteristics. Two published prediction models (the SOURCE model and Steyerberg model) were used to predict three-month survival for all patients included in the POLDER trial. Predicted survival probabilities were dichotomised and the accuracy, sensitivity, specificity, and the area under the curve (AUC) were used to evaluate the predictive performance.

Results: The SOURCE and Steyerberg model had an accuracy of 79% and 64%, and an AUC of 0.76 and 0.60 ($p = .017$), respectively. The SOURCE model had higher specificity across survival cut-off probabilities, the Steyerberg model had a higher sensitivity beyond the survival probability cut-off of 0.7. Using optimal cut-off probabilities, SOURCE would have wrongfully included 16/110 patients into the POLDER and Steyerberg 34/110.

Conclusion: The SOURCE model was found to be a more useful decision aid than the Steyerberg model. Results showed that the SOURCE model could be used for three-month survival predictions for patients that are considered for palliative treatment of dysphagia caused by oesophageal cancer in addition to clinicians' judgement.

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Introduction

Oesophageal cancer is the seventh most prevalent cancer in men and the 13th most commonly occurring cancer in women worldwide [1]. Roughly a third of patients with oesophageal cancer have a metastatic disease at primary diagnosis and the median overall survival (OS) ranges between 11 and 14 months [2–4]. Around 80–90% of oesophageal cancer patients report dysphagia during their clinical course [5,6]. In the recently published POLDER trial, it was shown that short course external beam radiotherapy (EBRT) was preferable over brachytherapy for palliation of dysphagia [7].

In the POLDER study, an estimated life expectancy of minimally three months was required for inclusion. However, about one-third of patients survived shorter. Survival estimates were based on clinical judgement of the treating physician. To aid in predicting survival for oesophageal cancer patients, various prediction models are available [8,9]. In the SIREC trial published in 2004, a total of 209 patients with dysphagia caused by incurable oesophageal cancer were randomised between intraluminal brachytherapy and stent placement. Based on these patients, a prediction tool for survival was developed by Steyerberg and colleagues [9]. More recently, the SOURCE prediction model was published based

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on 3271 metastatic oesophageal cancer patients [8]. Results show that the SOURCE model for metastatic oesophageal cancer patients demonstrates fair discrimination and good calibration. Although the SOURCE model is more recent and based on more patients, the Steyerberg model is based on patients treated for dysphagia only, and thus perhaps a better representative for this specific group.

The aim of the current study was to evaluate if the use of prediction tools would have improved survival prediction compared with clinical judgement in patients treated in the POLDER trial. In addition, the model's performances of predicting survival at three months will be used to determine which model is more suitable as a tool to determine which patients are eligible for EBRT treatment.

Methods

Study sample

This study is performed according to the TRIPOD checklist for the validation of prediction models [10]. The data used in the study originated from the POLDER study, a Dutch multicentre prospective cohort study of patients with metastasised or otherwise incurable oesophageal cancer requiring palliation of dysphagia between 2016 and 2019 [7]. The sample consisted of ($N = 115$) patients with incurable oesophageal $T_{2,\ 3,\ 4A,\ 4B,\ IS,X}$ $N_{0\text{-}3}M_{0\text{-}1}$ that were treated with EBRT in five fractions of 4 Gy. Patients with non-metastatic disease in poor condition and for whom treatment with curative intent was not deemed feasible were also included in the POLDER trial. The data were linked to the Netherlands Cancer Registry (NCR), a nation-wide database containing tumour, patient and treatment characteristics of patients diagnosed with cancer. Data from the NCR were used to retrieve the characteristics that were required for the prediction models but were not recorded in the POLDER study.

One patient was excluded from the analyses because this patient's T-stage was *in situ*. Four patients were excluded because the date of the start of their treatment was missing, thus leaving 110 patients for the analyses.

Furthermore, only the weight, but not the height of patients could be obtained due to practical constraints. To approximate patients' BMI, we used the average height of Dutch men and women as reported by Statistics Netherlands (CBS). For men this was 180.8 cm and for women this was 167.7 cm [11]. Additional sensitivity analyses were performed to investigate the effect of patient with a height of −10 cm and +10 cm.

Prediction models

The published SOURCE and Steyerberg prediction models were retrospectively used to predict three-month survival probabilities of patients treated in the POLDER trial. The SOURCE prediction model was recently developed for patients suffering from metastatic or potentially curable oesophageal or stomach cancer [8]. Since most patients treated in the POLDER trial had metastatic oesophageal cancer (87%), for the current study, the model for patients with metastatic oesophageal cancer was used. For the remaining 13% of patients without distant metastases, the general condition was considered too poor for curative or more radical treatment. Therefore, the model for metastatic patients was also used to predict survival for these 13% of patients. The predictors in the SOURCE model included the following patient characteristics: age, sex, body mass index, performance status, Albumin, LDH, Creatinine, type of treatment and the following tumour characteristics: cT and cN stage, differentiation grade, HER2 status, only distant lymph node metastases, peritoneal metastases, and number of metastatic sites.

The Steyerberg prediction model has been developed prior to the SOURCE prediction model and was intended to predict survival for oesophageal patients treated for dysphagia [9]. The predictors in the Steyerberg model differ from the SOURCE model. These predictors include the following patient characteristics: sex, age (per ten years), WHO performance status and tumour length. In this analysis, we fitted the cox regression model with the reported model's coefficients to the data. As the baseline hazard function was not reported by Steyerberg and colleagues, we estimated the baseline hazard on the POLDER data on the assumption that patients in the POLDER study had similar characteristics as patients in the SIREC trial on which the Steyerberg model was developed.

As the primary aim of this study was to investigate to what extent both models would perform better than the clinician's survival predictions, the main focus was on predicting survival at three months. Furthermore, threshold probabilities were used to evaluate if a patient was predicted to be deceased or alive at three months: the survival cut-off probability. Since the choice of such a cut-off probability is arbitrary and was unknown at the time of patient inclusion, we used multiple cut-off probabilities to evaluate the models. For example, if the cut-off probability was at 0.7, we assumed that patients with lower and higher values than 0.7 were predicted to be deceased and alive, respectively.

Statistical analyses

Three-month survival probabilities were computed with the published model coefficients of the SOURCE and Steyerberg models using the Prediction Error Curves for Risk Prediction Models in Survival Analysis (PEC) package for R [12]. For each model, the area under the curve (AUC) was calculated and the difference of the AUC between the SOURCE and Steyerberg model was tested for significance with a two-sided DeLong test with an alpha level of 0.05. The accuracy (the percentage of correct decisions), the sensitivity, and specificity were calculated to evaluate the models' predictions. To estimate the optimal cut-off survival probability, Youden's-index was used [13]. This method is developed to determine the optimal balance between sensitivity and specificity. Furthermore, the sensitivity and specificity for all cut-off scores between 0.5 and 1.0 were plotted and smoothed

Table 1. Descriptive statistics of the included patients.

Overall	
N	110
Tumour length > 10 cm (%)	6 (5.5)
Peritoneal metastases (%)	
No	87 (79.1)
Yes	2 (1.8)
Missing	21 (19.1)
Age (mean (SD))	71.36 (9.36)
Sex = Female (%)	25 (22.7)
BMI (mean (SD))	24.11 (4.66)
WHO performance status (%)	
0	20 (18.2)
1	37 (33.6)
2	20 (18.2)
3+	6 (5.5)
Missing	27 (24.5)
Albumine (mean (SD))	36.70 (5.27)
LDH (mean (SD))	227.91 (121.32)
Creatinine (mean (SD))	86.22 (27.58)
Clinical M-stage = 1 (%)	89 (80.9)
Clinical T-stage (%)	
2	37 (33.6)
3	48 (43.6)
4	9 (8.2)
X	16 (14.5)
Clinical N-stage (%)	
0	12 (10.9)
1	38 (34.5)
2	47 (42.7)
3	13 (11.8)
Differentation grade (%)	
G1	3 (2.7)
G2	24 (21.8)
G3	43 (39.1)
Missing	40 (36.4)
HER2 status (%)	
Negative	43 (39.1)
Positive	10 (9.1)
Missing	57 (51.8)
Only lymph node metastases (%)	
No	69 (62.7)
Yes	20 (18.2)
Missing	21 (19.1)
Number of metastases (%)	
0	21 (19.1)
1	45 (40.9)
2	27 (24.5)
3	17 (15.5)
First line treatment (%)	
Chemoradiation	31 (28.2)
Chemotherapy	4 (3.6)
Other	1 (0.9)
Radiotherapy metastases	1 (0.9)
Radiotherapy of primary tumour	73 (66.4)

using locally estimated scatterplot smoothing (LOESS). All analyses were performed in R version 4.0.3 [14].

Robustness

Missing data on the variables in the dataset were imputed *via* random forest imputation using the missForest package in R [15]. Missing forest imputation with missForest can handle missing values in data with different types of variables, complex interactions between variables and has been found to outperform other imputation methods such as multivariate imputation by chained equations in biological and medical datasets [15]. In addition, the missForest algorithm also provides an out of bag error estimate to evaluate the imputation error. This error is estimated by iteratively training the algorithm on a bootstrapped sample and testing on a number of complete cases that are not in the bootstrapped sample. The difference between observed and expected is defined as the out of bag error estimate.

Furthermore, to evaluate optimism of estimating the optimal cut-off and testing the model on the same data, we used 20 repeated five-fold cross validations [16]. This emulates the procedure of validating the cut-off probability with new data. For each repetition, the data were randomly partitioned into five folds. Four-folds were used for determining the optimal cut-off probability and one-fold was used for testing. This was repeated five times so that every patient was in the training and test fold at least one. The process of five-fold cross validation was repeated 20 times to increase stability of the estimates. The mean accuracy with 95% confidence interval was evaluated.

Table 2. Correct and incorrect in- and exclusions based on optimal cut-off probabilities.

	POLDER trial ($N = 110$)	SOURCE (cut-off probability = 0.70)	Steyerberg (cut-off probability = 0.87)
Wrongfully included	35	16	34
Wrongfully excluded	–	7	6
Correctly included	75	68	69
Correctly excluded	–	19	1

Results

Characteristics of patients treated in the POLDER study are shown in Table 1. Three months after the onset of treatment, 35 patients were deceased. The AUC of the SOURCE and Steyerberg models were 0.76 and 0.60, respectively ($p = .017$). Based on Youden's index, the optimal survival probability cut-off was 0.70 and 0.87 for the SOURCE and Steyerberg model, respectively. Using 0.70 as a cut-off, the accuracy of the SOURCE model was 79%, the sensitivity was 93%, and the specificity was 54%. Using 0.87 as a cut-off, the accuracy of the Steyerberg model was 64%, the sensitivity was 67%, and the specificity was 51%.

Table 2 shows how many patients would have been justly and unjustly included if the decision was only based on predicted survival using ideal cut-off probabilities. Retrospectively, SOURCE would have wrongfully included in total 16 patients as opposed to 35 patients that were wrongfully included in the POLDER trial. Steyerberg would have wrongfully included 34 patients.

Extending beyond the optimal survival cut-offs, the general trend was that the sensitivity of the SOURCE model was lower compared with the Steyerberg model (Figure 1) across cut-off probabilities higher than 0.7. The SOURCE model's specificity was higher than the Steyerberg model across all cut-off probabilities. Additionally, Figure 1 can be used to investigate the sensitivity and specificity given a different cut-off probability.

A nomogram of the SOURCE model (Figure 2) can be used to obtain the three month survival probability.

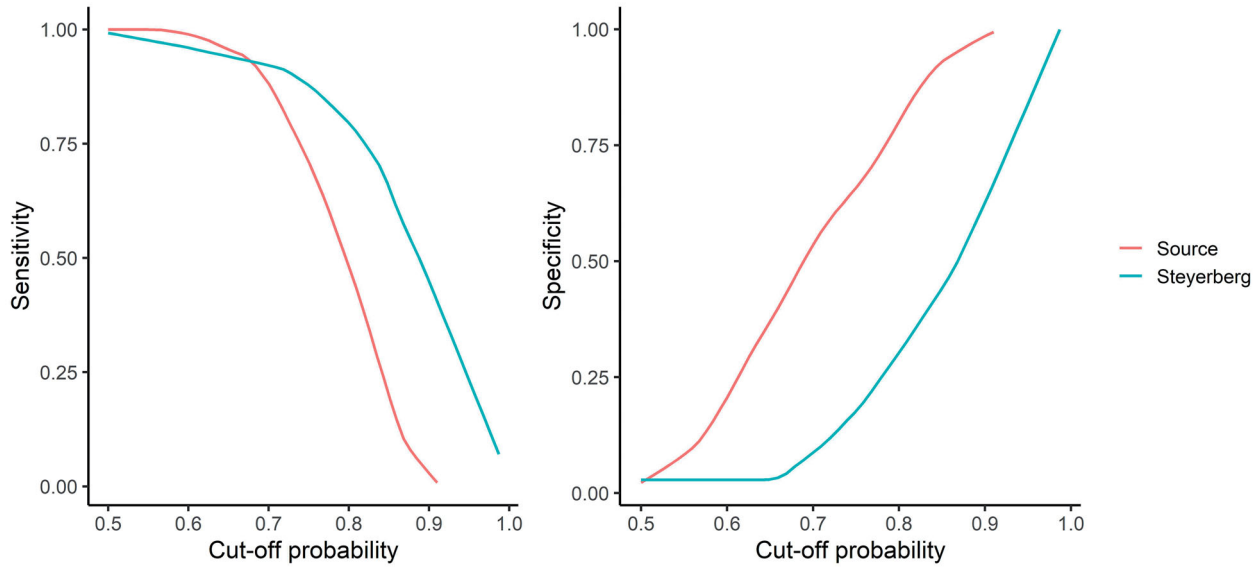

Figure 1. Sensitivity and specificity of the SOURCE and Steyerberg model as function of cut-off survival probability.

Robustness

After 20 five-fold cross validations, the accuracy of the SOURCE model was 0.74 (0.54–0.94) and 0.53 (0.31–0.75) for the Steyerberg model. Thus, the optimism of retrospectively estimating the cut-off probability of both models was 5% and 11% for SOURCE and Steyerberg, respectively.

Furthermore, the imputation error and the effect of varying the average patient height for the BMI calculation were separately tested. The normalised root mean squared error, which reflects the imputation error of continuous variables, was 2.52×10^{-7}. The proportion of falsely classified entries, which reflects the imputation error of categorical variables, was 0.15. Values close to zero indicate low imputation error, whereas values near one indicate high imputation error. Thus, the overall imputation error was low.

In additional sensitivity analyses, varying patients' average height with -10 cm and $+10$ cm had no effect on overall results (Supplementary Table 1). Therefore, for all analyses, heights of 180.8 cm for men and 167.7 cm for women were used to calculate BMI.

Discussion

The POLDER trial investigated the effects of EBRT on dysphagia caused by incurable oesophageal cancer [7]. Both the SOURCE and Steyerberg prediction models might have improved survival predictions for these patients in addition to the clinicians' judgement, albeit with different predictive characteristics.

Overall, the SOURCE model displayed a higher accuracy than the Steyerberg model. Furthermore, the SOURCE model was a more specific prediction model, whereas the Steyerberg model was more sensitive. This implies that when the SOURCE model would have been used as a decision aid, less patients in the POLDER trial would have been included that did not meet the criteria of surviving three months. On the other hand, this also implies that if the SOURCE model was used, some patients would not have been included but did survive three months. Based on the retrospectively estimated survival-cut-off scores, the SOURCE model outperformed the Steyerberg model because fewer patients would have been incorrectly included. Based on the prediction models only, SOURCE would have incorrectly included 16 patients and Steyerberg 34 patients.

Clinical implications

There is considerable treatment variation for patients with oesophageal cancer in the palliative setting [3,17,18]. For example, a significant hospital variation in treating patients with either EBRT or stent placement has been observed [19]. In daily practice, when the patient is considered for stent placement to relieve dysphagia, the SOURCE model can be used to determine whether EBRT treatment would be a good alternative. SOURCE outperforms the Steyerberg model in filtering patients that are likely to survive three months and as such identify patients for whom EBRT would be a good treatment option. In this scenario, the Steyerberg model would incorrectly select more patients for EBRT treatment.

For relieving dysphagia, treating patients with EBRT when they will not survive three months is undesirable, since the effect of EBRT on dysphagia relief is not immediate and patients will thus potentially not experience its effect [7]. These patients will likely benefit more from stent placement, which relieves dysphagia more rapidly [20]. Therefore, for patients that are likely to die soon or patients for whom it is unclear whether they will survive three months, stent placement is potentially a better option.

Inherent to SOURCE's conservative survival predictions, some patients will not receive EBRT treatment when they are alive after three months. This is the cost of using conservative survival predictions. However, making this error has less severe consequences for patients since these patients may have experienced rapid dysphagia relief and retreatment

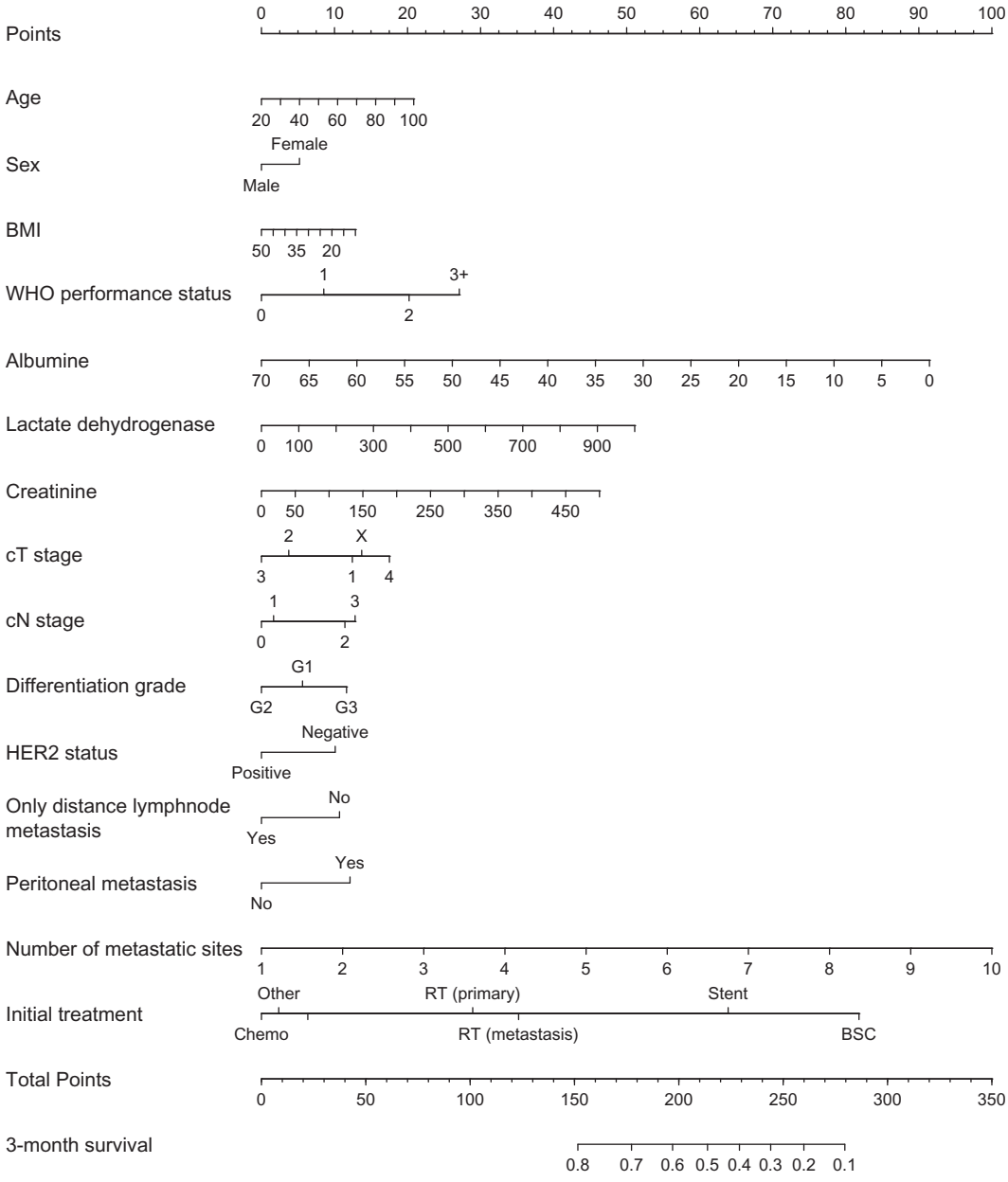

Figure 2. Nomogram for three-month survival of the SOURCE prediction model for metastatic patients. The SOURCE prediction model for patients with metastatic oesophageal cancer was developed on 3271 patients [8].

with stent replacement and can be performed when necessary [21]. Alternatively, stent removal and subsequent EBRT can be considered. Nevertheless, dysphagia recurrence after stent placement is high (31%) and possibly negatively impacts quality of life [22]. For practical application of the SOURCE model, the three-month survival nomogram for patients with metastatic oesophageal cancer (Figure 2) can be used.

For clinical application of the SOURCE and Steyerberg prediction models, the optimal cut-off probability can be used as this maximises the model accuracy, However, Figure 1 can also be used to visually inspect and select a different cut-off probability given desired sensitivities and specificities, as an alternative to the cut-off point based on the Youden index.

Strengths and limitations

This study has a number of strengths. First, it concerns a specific patient group in which research is rarely performed. Also, the data of this study were based on recent patient data. Moreover, multiple steps were undertaken to evaluate robustness of results. We conducted a repeated cross-validation to evaluate the optimism of estimating the cut-off probability and testing the model on the same data with that cut-off. To improve stability of the estimates, we repeated 5-fold cross-validation 20 times, which showed that overfitting of the cut-off probability was fairly low. Furthermore, even though we imputed missing data and calculated BMI using average heights' of men and women,

analyses showed that these missing data methods did not affect our conclusions.

A limitation of this study was that only treated patients were included in the POLDER study and thus the analysis. Unfortunately, data of excluded patients were not available. A second limitation was that we could not use the baseline survival hazard of the Steyerberg model because this was not reported. Alternatively, we used the baseline survival hazard of the patients of the POLDER trial. Patients in the POLDER trial were similar to patients in the SIREC trial on which the Steyerberg model was developed as the inclusions criteria were the same [23]. We therefore assumed similarity of their baseline survival hazard. Furthermore, patients in the POLDER trial were registered in the NCR and as such used to develop the SOURCE model. Overfitting was a potential hazard; however, the patients in the POLDER trial were only 3% of all patients used for fitting the SOURCE model. Thus, the risk of overfitting was relatively low.

Conclusion

Both the SOURCE and Steyerberg models could have improved three-month survival predictions in addition to clinical judgement alone for patients with incurable oesophageal cancer experiencing dysphagia. The SOURCE model was found to be a more useful decision aid than the Steyerberg model as it was more accurate, albeit slightly more conservative. Results showed that the SOURCE model could be used for patients that are considered for palliative treatment of dysphagia caused by oesophageal cancer.

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Data availability statement

Data is available from the Netherlands Cancer Registry.

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