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Original article

Nomogram for predicting pathologically complete response after neoadjuvant chemoradiotherapy for oesophageal cancer

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ABSTRACT

Background: A pathologically complete response (pCR) to neoadjuvant chemoradiotherapy (nCRT) is seen in 30% of the patients with oesophageal cancer. The aim is to identify patient and tumour characteristics associated with a pCR and to develop a nomogram for the prediction of pCR.

Patients and methods: Patients who underwent nCRT followed by surgery were identified and response to nCRT was assessed according to a modified Mandard classification in the resection specimen. A model was developed with age, gender, histology and location of the tumour, differentiation grade, alcohol use, smoking, percentage weight loss, Charlson Comorbidity Index (CCI), cT-stage and cN-stage as potential predictors for pCR. Probability of pCR was studied via logistic regression. Performance of the prediction nomogram was quantified using the concordance statistic (*c*-statistic) and corrected for optimism.

Results: A total of 381 patients were included. After surgery, 27.6% of the tumours showed a pCR. Female sex, squamous cell histology, poor differentiation grade, and low cT-stage were predictive for a pCR with a *c*-statistic of 0.64 (corrected for optimism).

Conclusion: A nomogram for the prediction of pathologically complete response after neoadjuvant chemoradiotherapy was developed, with a reasonable predictive power. This nomogram needs external validation before it can be used for individualised clinical decision-making.

Oesophageal cancer is an aggressive disease, with rising incidences in the United States and Western Europe [1,2]. It is often diagnosed at an advanced stage; hence less than half of the patients are eligible for potentially curative treatment. Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is considered standard treatment for locoregional disease (cT1N1 and cT2-T4a, N0-N3, M0). The purpose of this multimodality approach is to downstage the primary tumour and regional lymph nodes in order to facilitate a radical resection and to eradicate micrometastases. Recently, the Dutch CROSS trial showed that patients who underwent nCRT followed by surgery had a better survival with reduced locoregional and distant recurrences as compared to surgery alone [3–6].

The extent of tumour regression in the resection specimen, as assessed by the pathologist, in the primary lesion and removed lymph nodes is associated with survival after oesophagectomy [7,8]. Approximately 30% of patients receiving nCRT followed by surgery have a pathologically complete response (pCR; i.e. no vital tumour cells in the resection specimen) [6]. Patients with pCR have a better overall survival compared to patients with residual disease in the resection specimen [4,9–11]. Patients without substantial pathological response to nCRT do not seem to benefit from nCRT but are exposed to toxicity of nCRT. Furthermore, curative surgery is delayed [12].

Identification of patients who will benefit most from nCRT has been the subject of several studies. If we were able to accurately predict pCR in individual patients, these patients might be candidates to postpone or even omit surgical resection. Biomarker and tumour genetic profiles have been investigated, but they are complex to use and none have been properly validated. Functional imaging, including positron emission tomography is moderately able to identify responders early during neoadjuvant chemotherapy, but is less accurate for the early assessment of tumour response to nCRT [13,14].

The aim of this retrospective cohort study was to identify patient and tumour characteristics that are associated with

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pathologically complete response after nCRT. Secondly, we sought to develop a nomogram that is able to predict pathologically complete response in an attempt to identify potential patients in whom subsequent resection might be postponed or even omitted.

Patients and methods

Patients

A total of 381 patients with histologically proven carcinoma of the intrathoracic oesophagus or gastro-oesophageal junction who underwent nCRT according to CROSS between January 2002 and December 2013 followed by oesophagectomy, were identified from a prospectively collected database. The majority of the patients were treated at the Erasmus MC ($n = 255$, 66.9%), University Medical Centre Rotterdam, which is a tertiary referral centre for patients with oesophageal carcinoma in the Netherlands. The remaining patients ($n = 126$, 33.1%) were treated between 2004 and 2008 in one of the centres, which participated in the randomised CROSS trial [6]. Ethical approval was not required because of the retrospective character of the study as judged by the ethical committee of the Erasmus MC.

Staging

Tumours were (re-)staged according to the 7th UICC-AJCC TNM staging manual [15]. All patients underwent physical examination and routine haematological and biochemical tests. An upper gastro-intestinal endoscopy with biopsies, endoscopic ultrasonography (EUS) with fine needle aspiration (FNA) when indicated, computed tomography (CT) of the neck, chest and abdomen and external ultrasonography of the neck with FNA in case of suspected lymph nodes was performed in every patient. Bronchoscopy was only indicated for tumours with suspected infiltration of the tracheobronchial tree. Positron emission tomography (PET) was used in selected cases, but was not (yet) incorporated in the pretreatment staging of all patients of the study.

Selection of clinical parameters

Based on the cohort size, a maximum of 11 predictive parameters was allowed to be selected for response prediction. Selection of parameters was partly based on previously published literature and partly on generally accepted eligible criteria for nCRT followed by surgery [3,16–18].

Neoadjuvant chemoradiotherapy

Chemoradiotherapy prior to surgery was given within 5 weeks after completion of clinical staging and discussing the patient in the multidisciplinary team meetings. On days 1, 8, 15, 22, and 29, Carboplatin and Paclitaxel (targeted at an area under the curve of 2 mg per millilitre per minute and at a dose of 50 mg per square metre of body-surface area respectively) were administered intravenously. Concurrent with this chemotherapy a total 3D conformal radiation dose of 41.4 Gy (Gray) was given in 23 fractions of 1.8 Gy each, with 5 fractions administered per week, starting on the first day of the first chemotherapy cycle.

Surgery

All operations were performed or strictly supervised by experienced upper GI surgeons. For tumours substantially involving the gastro-oesophageal junction or in patients with a poor performance status (WHO performance score of 2 or higher), a transhiatal resection was favoured [19,20]. A transthoracic approach with two-field lymph node dissection was generally performed for tumours of the intrathoracic oesophagus and for junctional tumours with positive lymph nodes at or above the carina. A dissection of the nodes along the coeliac axis and its branches was carried out in both approaches. A gastric tube reconstruction with cervical anastomosis was the preferred technique for restoring the continuity of the digestive tract.

Pathological response evaluation

The fresh resection specimens were sent to the Department of Pathology and immediately examined by the attending pathologist. Samples of the tumour, lymph nodes and resection margins were obtained before the specimen was fixed in formalin. The tumour was staged according to the 7th UICC-AJCC TNM staging manual [15]. A radical resection (ypR0) was defined as no tumour cells within 1 mm of the circumferential, proximal or distal resection margins. Hence, when tumour cells were detected at or within 1 mm of the resection plane it was classified as ypR1. The number of lymph nodes removed and the number of tumour positive lymph nodes removed were recorded.

The tumour regression grade (TRG), used to assess the response to nCRT was classified into four categories according to the modified Mandard score: TRG 1, no vital tumour cells in the resection specimen (pCR of the primary tumour and removed lymph nodes, ypT0N0M0); TRG 2, less than 10% vital residual tumour cells and/or any vital residual tumour cells in the lymph nodes; TRG 3, between 10% and 50% vital residual tumour cells; and TRG 4, more than 50% vital residual tumour cells [21,22]. A single pathologist evaluated all the resection specimens.

Statistical analysis

The patient characteristics considered for the development of the prediction model were selected from the literature and from clinical experience [3,16–18]. The following parameters were considered to be potentially predictive for pCR: age at diagnosis, gender, histology and location of the tumour, differentiation grade, alcohol use, smoking, percentage weight loss, Charlson Comorbidity Index (CCI) [23], cT-stage of the tumour and cN-stage of the tumour.

Differentiation grade of the tumour was dichotomised in poorly differentiated vs. moderately and well differentiated. Alcohol use was divided into none, $\leqslant 2$ units per day and >2 units per day. Smoking contained three categories; none-smoking or stopped, sporadically smoking and heavily smoking (more than half a package of cigarettes per day). CCI was dichotomised into none vs. one or more comorbidities. cT-stage was coded as cT1/T2 vs. cT3/T4 and cN-stage was coded as cN0, cN1 or N2/N3. Frequencies of the individual parameters were calculated using SPSS statistical software (Version 22; IBM SPSS Inc., Armonk, NY, USA).

In the database 25% of patients had missing values for differentiation grade. For alcohol use and smoking, the percentage of missing values was 1%. For cT-stage and cN-stage, 4 (1%) and 5 (1.3%) patients respectively had missing data. Missing data were imputed 5 times using the multivariate imputation by chained equations (*mice*) algorithm [24].

Logistic regression was used to estimate univariable and multivariable regression coefficients and odds ratios with 95% confidence intervals for each selected parameter. The association between continuous parameters (i.e. age and percentage weight loss) and the probability of pCR was studied with restricted cubic splines with three knots [25]. The restricted cubic splines were approximated with simple transformations.

A full prediction model with all parameters included transformation was fitted in a complete dataset. Rubin's rules were used

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