Prediction of survival in patients with oesophageal or junctional cancer receiving neoadjuvant chemoradiotherapy and surgery

J. Shapiro[1], D. van Klaveren[2], S. M. Lagarde[1,4], E. L. A. Toxopeus[1], A. van der Gaast[3], M. C. C. M. Hulshof[5], B. P. L. Wijnhoven[1], M. I. van Berge Henegouwen[4], E. W. Steyerberg[2] and J. J. B. van Lanschot[1]

Departments of [1] Surgery, [2] Public Health and [3] Medical Oncology, Erasmus MC – University Medical Centre, Rotterdam, and Departments of [4] Surgery and [5] Radiotherapy, Academic Medical Centre, Amsterdam, The Netherlands

Correspondence to: Mr J. Shapiro, Department of Surgery, Suite H-812, Erasmus MC – University Medical Centre Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands (e-mail: j.shapiro@erasmusmc.nl)

Background: **The value of conventional prognostic factors is unclear in the era of multimodal treatment for oesophageal cancer. This study aimed to quantify the impact of neoadjuvant chemoradiotherapy (nCRT) and surgery on well established prognostic factors, and to develop and validate a prognostic model.**

Methods: **Patients treated with nCRT plus surgery were included. Multivariable Cox modelling was used to identify prognostic factors for overall survival. A prediction model for individual survival was developed using stepwise backward selection. The model was internally validated leading to a nomogram for use in clinical practice.**

Results: **Some 626 patients who underwent nCRT plus surgery were included. In the multivariable model, only pretreatment cN category and ypN category were independent prognostic factors. The final prognostic model included cN, ypT and ypN categories, and had moderate discrimination (c-index at internal validation 0·63).**

Conclusion: **In patients with oesophageal or oesophagogastric cancer treated with nCRT plus surgery, overall survival can best be estimated using a prediction model based on cN, ypT and ypN categories. Predicted survival according to this model showed only moderate correlation with observed survival, emphasizing the need for new prognostic factors to improve survival prediction.**

Presented in part to the 14th World Congress of the International Society for Diseases of the Esophagus, Vancouver, British Columbia, Canada, September 2014

Paper accepted 3 February 2016

Published online 26 April 2016 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10142

Introduction

In patients with cancer of the oesophagus or oesophagogastric junction, several pretreatment prognostic factors have been identified for those undergoing primary surgical resection. These include age[1,2], sex[2–5], weight loss[6,7], histological tumour subtype[8,9], tumour location[10–12], tumour length[13–15] and clinical TNM stage[16,17]. Well established prognostic factors that become available after oesophagectomy include surgical approach[18,19], surgical radicality[20–22], degree of tumour differentiation[8,23] and pathological TNM stage[12,24]. Models have been developed to predict overall survival in individual patients, based on these factors[25,26], although most have been identified and validated in the era of primary surgical resection.

Recent studies show that the addition of neoadjuvant chemoradiotherapy (nCRT) to surgery improves locoregional control and long-term survival compared with surgery alone[27,28]. The value of conventional prognostic factors and the accuracy of models for individual survival prediction are still unclear, however, in the context of current multimodal treatment strategies.

The aims of this study were to assess the value of prognostic factors in relation to patients undergoing nCRT and surgery for oesophageal or junctional cancer, and to develop and validate a prognostic model for these patients.

Methods

Patients treated with nCRT plus surgery as part of the single-centre non-randomized CROSS-I trial[29] (2001–2004), with nCRT plus surgery as part of the multicentre randomized clinical CROSS-II trial[28] (2004–2009),

Table 1 Clinical, surgical and histopathological characteristics of patients with potentially curable carcinoma of the oesophagus or oesophagogastric junction, treated with neoadjuvant chemoradiotherapy plus surgery, 2001–2013

		nCRT + surgery (*n* = 626)
Age (years)*		63 (56–69)
Sex ratio (F : M)		134 : 492
Weight loss (kg)* (*n* = 607)		3 (0–6)
Tumour histology†	Squamous cell carcinoma	139 (22·2)
	Adenocarcinoma	481 (76·8)
	Indeterminable	6 (1·0)
Tumour location‡	Upper third	3 (0·5)
	Middle third	81 (13·0)
	Lower third	413 (66·4)
	Oesophagogastric junction	125 (20·1)
	Missing	4
Tumour length‡ (cm)* (*n* = 579)		5 (3–6)
Clinical T category§	cT1	12 (2·0)
	cT2	113 (18·5)
	cT3	476 (77·9)
	cT4	10 (1·6)
	Missing	15
Clinical N category§	cN0	182 (29·7)
	cN1	430 (70·3)
	Missing	14
Surgical approach	Transhiatal	224 (35·8)
	Transthoracic	397 (63·4)
	Other	5 (0·8)
Radicality¶	R0	589 (94·1)
	R1	37 (5·9)
Degree of tumour differentiation#	Gx (indeterminable)	171 (36·3)
	G1	9 (1·9)
	G2	133 (28·2)
	G3	158 (33·5)
	Missing	155
Post-treatment pathological T category**	ypT0	187 (29·9)
	ypT1 (includes pTis)	89 (14·2)
	ypT2	106 (16·9)
	ypT3	240 (38·3)
	ypT4	4 (0·6)
Post-treatment pathological N category**	ypN0	400 (63·9)
	ypN1	146 (23·3)
	ypN2	60 (9·6)
	ypN3	20 (3·2)
Tumour regression grade††	TRG1	187 (30·1)
	TRG2	135 (21·7)
	TRG3	175 (28·2)
	TRG4	124 (20·0)
	Missing	5

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Determined from pretreatment biopsy. ‡Determined by endoscopy. §Determined by endoscopic ultrasonography and CT with or without fluorodeoxyglucose-PET according to the sixth edition of the International Union Against Cancer (UICC) TNM classification[30]: cT1, (sub)mucosal involvement; cT2, proper muscle layer involvement; cT3, surrounding stroma involvement. ¶R0 defined as a tumour-free resection margin of at least 1 mm; R1 defined as a macroscopically radical resection, with a microscopically tumour-free resection margin of less than 1 mm. #Determined in the resection specimen only; histological degree of tumour differentiation was not determined in the pretreatment biopsy. **pT and pN categories, as measured in the resection specimen, were (re)scored according to the seventh edition of the UICC TNM classification[31]: ypT1, (sub)mucosal involvement; ypT2, proper muscle layer involvement; ypT3, surrounding stroma involvement; ypN0, no lymph node positivity; ypN1, one or two positive lymph nodes; ypN2, three to six positive lymph nodes; ypN3, seven or more positive lymph nodes. ††Scored as defined by Chirieac *et al.*[32,33]: TRG1, no residual tumour cells found; TRG2, 1–10 per cent residual tumour cells; TRG3, 11–50 per cent residual tumour cells; TRG4, more than 50 per cent residual tumour cells. nCRT, neoadjuvant chemoradiotherapy.

or with nCRT plus surgery as standard of care at the Erasmus MC, Rotterdam, or the Academic Medical Centre, Amsterdam (post-CROSS, 2009–2013) were included. Both squamous cell carcinoma and adenocarcinoma histologies were included. Patients who did not receive at least 80 per cent of the planned dose of chemoradiotherapy, who received a nCRT regimen other than CROSS or in whom surgical resection was not completed were excluded.

Clinical staging

Pretreatment staging included: endoscopy with biopsy, endoscopic ultrasonography (with fine-needle aspiration (FNA) when indicated); CT of the neck, chest and abdomen; and external ultrasonography of the neck (with FNA when indicated). PET was not performed routinely during this study, only when conventional endoscopic ultrasound imaging and CT showed signs of extensive lymph node involvement, to obtain further assurance of the absence of distant dissemination. Tumour location and length were determined by pretreatment endoscopy. cT and cN categories were determined by endoscopic ultrasonography and CT with or without fluorodeoxyglucose-PET according to the sixth edition of the International Union Against Cancer (UICC) TNM classification[30].

Neoadjuvant and surgical treatment

For carcinomas at or above the level of the carina, a transthoracic oesophagectomy (TTO) with two-field lymph node dissection was performed. For carcinomas located well below the level of the carina, either TTO with two-field lymph node dissection or transhiatal oesophagectomy (THO) was performed, depending on fitness of the patient and surgeon preference. For carcinomas involving the oesophagogastric junction, THO was the preferred technique. For both the transthoracic and transhiatal approach, an upper abdominal lymphadenectomy was performed, including resection of nodes along the hepatic artery, splenic artery and origin of the left gastric artery. Open as well as minimally invasive techniques were used.

Pathological assessment

Tumour type was determined from the pretreatment biopsy, whereas degree of tumour differentiation was determined in the resection specimen. In the absence of residual tumour in the resection specimen, degree of tumour differentiation was scored as indeterminable (Gx). A microscopically radical resection (R0) was defined as a tumour-free resection margin of at least 1 mm. R1 was defined as a macroscopically radical resection, with a microscopically tumour-free resection margin of less than 1 mm. pT and pN categories were (re)scored according to the seventh edition of the UICC TNM classification[31]. The tumour regression grade (TRG) was scored using the system as reported by Chirieac and co-workers[32,33].

Follow-up and data collection

Clinical and surgical characteristics were collected from prospectively developed institutional databases. Overall survival was assessed based on all-cause mortality, and determined using hospital records and municipal registers. Overall survival was truncated at 5 years to reduce the effect of death from other causes.

Statistical analysis

Data are described as median (i.q.r.) for continuous variables and as frequencies with percentages for categorical variables. Grouped data were compared using Student's t test and Pearson's χ^2 test. During imputation, missing data were assumed to be distributed in the same way as the rest of the data set[34]. Categories with fewer than 20 patients were combined with related categories. Weight loss during nCRT was truncated at 10 kg (95th percentile). During imputation, pT0 was set to combine with TRG1 and Gx. In the total patient cohort, hazard ratios (HRs), with corresponding 95 per cent confidence intervals (c.i.) were calculated using a multivariable Cox proportional hazards model. The following factors were selected on the basis of their usefulness in other studies and tested directly in a multivariable model: age, sex, weight loss, tumour histology, tumour location, tumour length, cT category, cN category, surgical approach, radicality of resection, degree of tumour differentiation in the resection specimen, ypT category, pN category and TRG. Overall survival was calculated from the end of therapy (day of surgery in both treatment groups) until death (from any cause) or end of follow-up.

Development, validation and visualization of prognostic model

A prognostic model was developed using stepwise backward selection, in which variables were excluded, testing for the significance of elimination per variable, until no further improvement was achieved[35]. The prognostic model was internally validated by correcting for optimism, and cross-validated by dividing the total nCRT plus surgery cohort into a cohort with patients from the

Table 2 Multivariable Cox analysis of prognostic factors for overall survival in 626 patients with potentially curable carcinoma of the oesophagus or oesophagogastric junction, treated with neoadjuvant chemoradiotherapy plus surgery, 2001–2013

	Hazard ratio	*P*
Age (per 10 years)	1·12 (0·98, 1·28)	0·099
Sex		
F	0·77 (0·55, 1·08)	0·129
M	1·00 (reference)	
Weight loss (per kg)	1·01 (0·98, 1·05)	0·462
Tumour histology		
Squamous cell carcinoma	0·77 (0·53, 1·12)	0·173
Adenocarcinoma	1·00 (reference)	
Tumour location		
Cervical to middle third oesophagus	1·00 (reference)	
Lower third oesophagus	0·93 (0·60, 1·44)	0·740
Oesophagogastric junction	0·72 (0·42, 1·23)	0·232
Tumour length (per cm)	0·97 (0·92, 1·04)	0·414
Clinical T category		
cT1–2	1·00 (reference)	
cT3–4	1·16 (0·81, 1·67)	0·415
Clinical N category		
cN0	1·00 (reference)	
cN1	1·46 (1·09, 1·95)	0·012
Surgical approach		
Transhiatal	1·00 (reference)	
Transthoracic or other	1·15 (0·87, 1·52)	0·333
Radicality		
R0	1·00 (reference)	
R1–2	1·35 (0·85, 2·15)	0·202
Degree of tumour differentiation		
Gx	1·94 (0·36, 8·61)	0·385
G1	1·00 (reference)	
G2	2·78 (0·58, 13·25)	0·202
G3	2·80 (0·67, 11·74)	0·159
Post-treatment pathological T category		
ypT0	0·76 (0·49, 1·17)	0·318
ypT1	1·00 (reference)	
ypT2	1·02 (0·64, 1·61)	0·945
ypT3–4	1·15 (0·76, 1·73)	0·499
Post-treatment pathological N category		
ypN0	1·00 (reference)	
ypN1	1·78 (1·32, 2·39)	< 0·001
ypN2	1·98 (1·29, 3·02)	< 0·001
ypN3	4·34 (2·38, 7·93)	< 0·001
Tumour regression grade*		
TRG1	0·77 (0·52, 1·12)	0·173
TRG2	1·00 (reference)	
TRG3	1·21 (0·85, 1·72)	0·302
TRG4	1·03 (0·69, 1·54)	0·895

Values in parentheses are 95 per cent confidence intervals. *Different groupings of tumour regression grade (TRG) were also tested: TRG1 *versus* TRG2–4[39], TRG1 *versus* TRG2–3 *versus* TRG4[41], and TRG1–2 *versus* TRG3–4[40] (data not shown); none of these groupings showed a significant independent effect.

Erasmus MC, Rotterdam, and a cohort with patients from all other centres. The model was tested for prognostic accuracy using Harrell's concordance index (c-index)[36]. The c-index determines, for two randomly chosen subjects, the probability that the model predicts a higher risk for the subject with poorer outcome. Analyses were performed using the following R packages[37]: 'multivariate imputation by chained equations' (mice)[34] and 'regression modeling strategies' (rms)[38].

A nomogram was created in which the weights for each category within an individual risk factor were calculated by multiplying the original coefficients of the multivariable

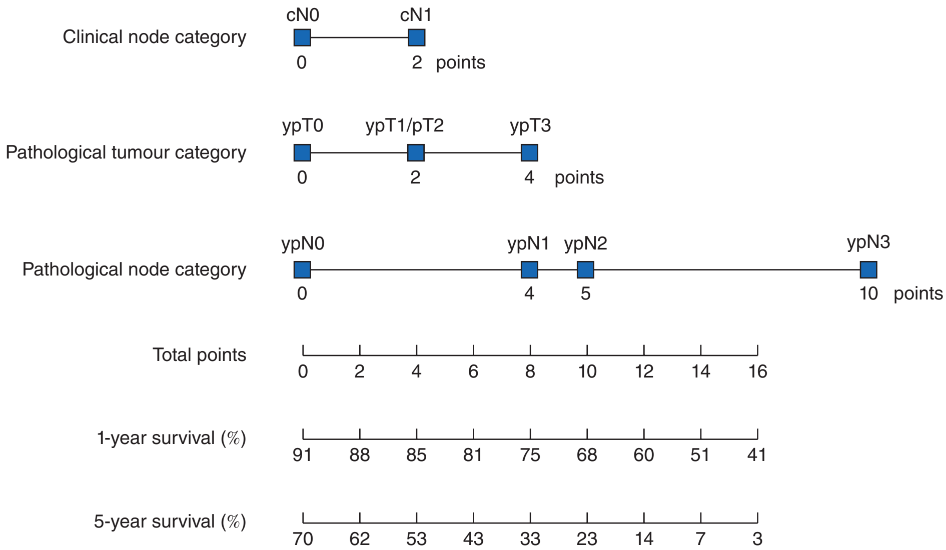

Fig. 1 Nomogram for overall survival as developed in 626 patients with potentially curable carcinoma of the oesophagus or oesophagogastric junction, treated with neoadjuvant chemoradiotherapy (nCRT) plus surgery. From the total points axis, a straight line down through the survival axes shows survival probabilities at 1 and 5 years. cN category according to the sixth edition of the International Union Against Cancer (UICC) TNM classification[30]: cN0, no clinical suspicion of pretreatment lymph node involvement; cN1, clinical suspicion of pretreatment lymph node involvement. ypT category according to the seventh edition of the UICC TNM classification[31]: ypT0, no residual tumour at the primary tumour site; ypT1, (sub)mucosal involvement; ypT2, proper muscle layer involvement; ypT3, surrounding stroma involvement. pN category according to the seventh edition of the UICC TNM classification[31]: ypN0, no lymph node positivity; ypN1, one to two positive lymph nodes; ypN2, three to six positive lymph nodes; ypN3, seven or more positive lymph nodes

Cox model by ten and rounding the result to the lowest whole number. The total number of points derived from all predictors was used to calculate expected 1- and 5-year overall survival rates.

Results

In the study period, 661 patients underwent nCRT according to CROSS followed by resection. Of these, 626 patients (94·7 per cent) had at least 80 per cent of the neoadjuvant regimen and were included for subsequent analysis. Median age at diagnosis was 63 years (*Table 1*). Most patients were men (77·8 per cent), and most had an adenocarcinoma (76·8 per cent), most often clinically staged as cT3 (77·9 per cent).

Prognostic factors

In patients treated with nCRT plus surgery, the only independent prognostic factors were cN category (HR 1·46, 95 per cent c.i. 1·09 to 1·95; $P = 0{\cdot}012$) and ypN category (ypN1: HR 1·78, 1·32 to 2·39, $P < 0{\cdot}001$; ypN2: HR 1·98, 1·29 to 3·02, $P < 0{\cdot}001$; ypN3: HR 4·34, 2·38 to 7·93, $P < 0{\cdot}001$) (*Table 2*). Specifically, TRG was not prognostic for survival (*Table 2*); this was also the case when different groupings of TRG[39–41] were tested (data not shown).

Prediction model for survival

After stepwise backward selection, the final prediction model included cN, ypT and ypN categories. Discrimination of the prediction model was moderate (c-index at internal validation 0·63). Cross-validation between the Erasmus MC cohort (246 patients) and the other centres (380) was comparable (c-index 0·62 and 0·63 respectively). A nomogram was constructed (*Fig. 1*) to allow individual 1- and 5-year overall survival estimations, based on the three variables included in the final prediction model. As an example, patients with pretreatment suspicion of nodal disease (cN1) and a complete response in the resection specimen (ypT0, ypN0) would have a total of 2 points, corresponding to estimated 1- and 5-year survival rates of 88 and 62 per cent respectively.

Discussion

Pretreatment cN category and post-treatment ypN category were the only independent prognostic factors in patients who underwent at least 80 per cent of nCRT plus surgery. ypT category was added to the final prediction model for these patients after backward selection.

ypN category was the most important prognostic factor in this study, confirming previous reports[42,43], and underlining the continued significance of pN category as an important prognostic factor in the era of multimodal treatment[42–45]. Surprisingly, cN category was an independent prognostic factor in patients treated with nCRT plus surgery, despite its relative inaccuracy[46,47]. By definition, cN category is an estimation of nodal involvement before nCRT, whereas ypN category is an estimation of nodal involvement after nCRT. In patients treated with surgery alone cN and pN categories estimate the same disease state, whereas in patients treated with nCRT plus surgery cN category no longer necessarily estimates the same disease state as ypN category, owing to the effects of nCRT. Therefore, in patients treated with nCRT plus surgery, cN and ypN categories are considered to represent different disease states, and cN category, although relatively inaccurate, still has additional prognostic value.

Another important finding was that surgical approach was no longer associated with survival in patients treated with nCRT plus surgery. This suggests that, in patients treated with nCRT plus surgery, the benefit of a transthoracic approach is at best limited and the necessity for maximization of surgical lymph node retrieval should be questioned. However, only a new randomized clinical trial, comparing these two surgical approaches (with their inherent differences in extent of lymphadenectomy) after neoadjuvant treatment, will offer a definitive answer.

The final prognostic model had moderate discriminatory ability, although this was lower than that generally reported for other tumour types after neoadjuvant treatment[48–50]. The present study did not identify any additional factors outside the TNM staging system that might contribute to more accurate prognostication related to multimodal treatment. In particular, TRG[32,33,39–41] was not significantly associated with survival in multivariable analysis. A strong and significant association of TRG with survival found at univariable analysis (data not shown) was completely lost with the addition of pN category only. This suggests that both factors are present in many of the same patients, and that pN category carries more prognostic information than TRG.

The study has limitations. The time interval for data collection was relatively long (2001–2013). PET–CT was used only in patients with extensive clinical lymph node involvement, in order to obtain further assurance that there were indeed no signs of distant dissemination. Such selective use of PET–CT might have introduced selection bias. The exact number of clinically suspected nodes was not recorded in many of the earlier patients in this cohort (before the introduction of the seventh edition of the UICC TNM classification[31]). Therefore, clinical nodal staging could be determined only for all patients according to the sixth edition of the TNM classification[30], which classified nodal disease only as positive or negative. This necessary categorization may have restricted the prognostic significance of pretreatment clinical nodal staging. Although a radical resection with clear margins (R0) demanded a tumour-free resection margin of at least 1 mm in the present study, the conclusions drawn regarding R status might not apply using the College of American Pathologists' methodology, where an R0 resection is defined as a tumour-free resection margin of 0 mm or more[51]. It must also be acknowledged that not all recognized prognostic factors in oesophageal and junctional cancer could be included in this study, such as extracapsular lymph node involvement[52–54], signet cell features in oesophageal adenocarcinomas[55,56] or genetic and molecular markers[57,58].

Although the overall survival of patients with oesophageal or junctional cancer treated with nCRT plus surgery can best be estimated using a prediction model based on cN, ypT and ypN categories, the moderate correlation between predicted and observed survival reinforces the need for novel prognostic factors to improve prediction of survival.

Acknowledgements

The authors are grateful to C. M. Vollebregt-Uiterwijk (Department of Surgery, Erasmus MC – University Medical Centre, Rotterdam) for her dedicated prospective data collection. The authors thank H. F. Lingsma (Department of Public Health, Erasmus MC – University Medical Centre, Rotterdam) and P. M. M. Bossuyt (Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, Amsterdam) for their assistance in study design, statistical analysis and interpretation of the data.

S.M.L. is supported by a Koningin Wilhelmina Fonds (Dutch Cancer Society) Fellowship (UVA 2013–5853).

Disclosure: The authors declare no conflict of interest.

References

1 Markar SR, Karthikesalingam A, Thrumurthy S, Ho A, Muallem G, Low DE. Systematic review and pooled analysis assessing the association between elderly age and outcome following surgical resection of esophageal malignancy. *Dis Esophagus* 2013; **26**: 250–262.

2 Chen MF, Yang YH, Lai CH, Chen PC, Chen WC. Outcome of patients with esophageal cancer: a nationwide analysis. *Ann Surg Oncol* 2013; **20**: 3023–3030.
3 Micheli A, Mariotto A, Giorgi Rossi A, Gatta G, Muti P. The prognostic role of gender in survival of adult cancer patients. EUROCARE Working Group. *Eur J Cancer* 1998; **34**: 2271–2278.
4 Ferri LE, Law S, Wong KH, Kwok KF, Wong J. The influence of technical complications on postoperative outcome and survival after esophagectomy. *Ann Surg Oncol* 2006; **13**: 557–564.
5 Micheli A, Ciampichini R, Oberaigner W, Ciccolallo L, de Vries E, Izarzugaza I *et al*. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. *Eur J Cancer* 2009; **45**: 1017–1027.
6 Polee MB, Hop WC, Kok TC, Eskens FA, van der Burg ME, Splinter TA *et al*. Prognostic factors for survival in patients with advanced oesophageal cancer treated with cisplatin-based combination chemotherapy. *Br J Cancer* 2003; **89**: 2045–2050.
7 D'Journo XB, Ouattara M, Loundou A, Trousse D, Dahan L, Nathalie T *et al*. Prognostic impact of weight loss in 1-year survivors after transthoracic esophagectomy for cancer. *Dis Esophagus* 2012; **25**: 527–534.
8 Khan OA, Alexiou C, Soomro I, Duffy JP, Morgan WE, Beggs FD. Pathological determinants of survival in node-negative oesophageal cancer. *Br J Surg* 2004; **91**: 1586–1591.
9 Gertler R, Stein HJ, Langer R, Nettelmann M, Schuster T, Hoefler H *et al*. Long-term outcome of 2920 patients with cancers of the esophagus and esophagogastric junction: evaluation of the New Union Internationale Contre le Cancer/American Joint Cancer Committee staging system. *Ann Surg* 2011; **253**: 689–698.
10 Christein JD, Hollinger EF, Millikan KW. Prognostic factors associated with resectable carcinoma of the esophagus. *Am Surg* 2002; **68**: 258–262.
11 Omloo JM, Lagarde SM, Hulscher JB, Reitsma JB, Fockens P, van Dekken H *et al*. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg* 2007; **246**: 992–1000.
12 Rice TW, Rusch VW, Ishwaran H, Blackstone EH. Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. *Cancer* 2010; **116**: 3763–3773.
13 Eloubeidi MA, Desmond R, Arguedas MR, Reed CE, Wilcox CM. Prognostic factors for the survival of patients with esophageal carcinoma in the U.S.: the importance of tumor length and lymph node status. *Cancer* 2002; **95**: 1434–1443.
14 Bollschweiler E, Baldus SE, Schröder W, Schneider PM, Holscher AH. Staging of esophageal carcinoma: length of tumor and number of involved regional lymph nodes. Are these independent prognostic factors? *J Surg Oncol* 2006; **94**: 355–363.
15 Griffiths EA, Brummell Z, Gorthi G, Pritchard SA, Welch IM. Tumor length as a prognostic factor in esophageal malignancy: univariate and multivariate survival analyses. *J Surg Oncol* 2006; **93**: 258–267.
16 Mariette C, Balon JM, Maunoury V, Taillier G, Van Seuningen I, Triboulet JP. Value of endoscopic ultrasonography as a predictor of long-term survival in oesophageal carcinoma. *Br J Surg* 2003; **90**: 1367–1372.
17 Omloo JM, Sloof GW, Boellaard R, Hoekstra OS, Jager PL, van Dullemen HM *et al*. Importance of fluorodeoxyglucose-positron emission tomography (FDG-PET) and endoscopic ultrasonography parameters in predicting survival following surgery for esophageal cancer. *Endoscopy* 2008; **40**: 464–471.
18 Lerut T, De Leyn P, Coosemans W, Van Raemdonck D, Scheys I, LeSaffre E. Surgical strategies in esophageal carcinoma with emphasis on radical lymphadenectomy. *Ann Surg* 1992; **216**: 583–590.
19 Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. *Ann Surg* 2002; **236**: 177–183.
20 Wijnhoven BP, Tran KT, Esterman A, Watson DI, Tilanus HW. An evaluation of prognostic factors and tumor staging of resected carcinoma of the esophagus. *Ann Surg* 2007; **245**: 717–725.
21 O'Farrell NJ, Donohoe CL, Muldoon C, Costelloe JM, King S, Ravi N *et al*. Lack of independent significance of a close (<1 mm) circumferential resection margin involvement in esophageal and junctional cancer. *Ann Surg Oncol* 2013; **20**: 2727–2733.
22 Wu J, Chen QX, Teng LS, Krasna MJ. Prognostic significance of positive circumferential resection margin in esophageal cancer: a systematic review and meta-analysis. *Ann Thorac Surg* 2014; **97**: 446–453.
23 Thompson SK, Ruszkiewicz AR, Jamieson GG, Esterman A, Watson DI, Wijnhoven BP *et al*. Improving the accuracy of TNM staging in esophageal cancer: a pathological review of resected specimens. *Ann Surg Oncol* 2008; **15**: 3447–3458.
24 Kim HI, Cheong JH, Song KJ, An JY, Hyung WJ, Noh SH *et al*. Staging of adenocarcinoma of the esophagogastric junction: comparison of AJCC 6th and 7th gastric and 7th esophageal staging systems. *Ann Surg Oncol* 2013; **20**: 2713–2720.
25 Lagarde SM, Reitsma JB, de Castro SM, Ten Kate FJ, Busch OR, van Lanschot JJ. Prognostic nomogram for patients undergoing oesophagectomy for adenocarcinoma of the oesophagus or gastro-oesophageal junction. *Br J Surg* 2007; **94**: 1361–1368.
26 Lagarde SM, Reitsma JB, Ten Kate FJ, Busch OR, Obertop H, Zwinderman AH *et al*. Predicting individual survival after potentially curative esophagectomy for adenocarcinoma of the esophagus or gastroesophageal junction. *Ann Surg* 2008; **248**: 1006–1013.
27 Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A *et al.*; Australasian Gastro-Intestinal Trials Group. Survival after neoadjuvant chemotherapy or

chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011; **12**: 681–692.
28 van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP *et al*. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074–2084.
29 van Meerten E, Muller K, Tilanus HW, Siersema PD, Eijkenboom WM, van Dekken H *et al*. Neoadjuvant concurrent chemoradiation with weekly paclitaxel and carboplatin for patients with oesophageal cancer: a phase II study. *Br J Cancer* 2006; **94**: 1389–1394.
30 Sobin LH, Wittekind C (eds). *TNM Classification of Malignant Tumors* (6th edn). Wiley–Liss: New York, 2002.
31 Sobin LH, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumors* (7th edn). Wiley–Blackwell: New York, 2009.
32 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.
33 Chirieac LR, Swisher SG, Ajani JA, Komaki RR, Correa AM, Morris JS *et al*. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* 2005; **103**: 1347–1355.
34 van Buuren S, Groothuis-Oudshoorn K, Robitzsch A, Vink G, Doove L, Shahab J. *Mice: Multivariate Imputation by Chained Equations*. R package version 2.22. R Foundation for Statistical Computing: Vienna, 2011.
35 Steyerberg EW. *Clinical Prediction Models. A Practical Approach to Development, Validation, and Updating*. Springer: New York, 2009.
36 Harrell FE Jr. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. Springer: New York, 2001.
37 R Development Core Team. *R: a Language and Environment for Statistical Computing* (3.0.2 edn). R Foundation for Statistical Computing: Vienna, 2013.
38 Harrell FE Jr. *RMS: Regression Modeling Strategies*. R package version 3.6-3. R Foundation for Statistical Computing: Vienna, 2013.
39 Donington JS, Miller DL, Allen MS, Deschamps C, Nichols FC III, Pairolero PC. Tumor response to induction chemoradiation: influence on survival after esophagectomy. *Eur J Cardiothorac Surg* 2003; **24**: 631–636.
40 Schneider PM, Baldus SE, Metzger R, Kocher M, Bongartz R, Bollschweiler E *et al*. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. *Ann Surg* 2005; **242**: 684–692.
41 Donohoe CL, O'Farrell NJ, Grant T, King S, Clarke L, Muldoon C *et al*. Classification of pathologic response to neoadjuvant therapy in esophageal and junctional cancer: assessment of existing measures and proposal of a novel 3-point standard. *Ann Surg* 2013; **258**: 784–792.
42 Gu Y, Swisher SG, Ajani JA, Correa AM, Hofstetter WL, Liao Z *et al*. The number of lymph nodes with metastasis predicts survival in patients with esophageal or esophagogastric junction adenocarcinoma who receive preoperative chemoradiation. *Cancer* 2006; **106**: 1017–1025.
43 Rizk NP, Venkatraman E, Bains MS, Park B, Flores R, Tang L *et al*. American Joint Committee on Cancer staging system does not accurately predict survival in patients receiving multimodality therapy for esophageal adenocarcinoma. *J Clin Oncol* 2007; **25**: 507–512.
44 Ajani JA, Correa AM, Swisher SG, Wu TT. For localized gastroesophageal cancer, you give chemoradiation before surgery, but then what happens? *J Clin Oncol* 2007; **25**: 4315–4316.
45 Holscher AH, Drebber U, Schmidt H, Bollschweiler E. Prognostic classification of histopathologic response to neoadjuvant therapy in esophageal adenocarcinoma. *Ann Surg* 2014; **260**: 779–784.
46 van Vliet EP, Eijkemans MJ, Kuipers EJ, Poley JW, Steyerberg EW, Siersema PD. Publication bias does not play a role in the reporting of the results of endoscopic ultrasound staging of upper gastrointestinal cancers. *Endoscopy* 2007; **39**: 325–332.
47 van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer* 2008; **98**: 547–557.
48 Rouzier R, Pusztai L, Delaloge S, Gonzalez-Angulo AM, Andre F, Hess KR *et al*. Nomograms to predict pathologic complete response and metastasis-free survival after preoperative chemotherapy for breast cancer. *J Clin Oncol* 2005; **23**: 8331–8339.
49 Quah HM, Chou JF, Gonen M, Shia J, Schrag D, Saltz LB *et al*. Pathologic stage is most prognostic of disease-free survival in locally advanced rectal cancer patients after preoperative chemoradiation. *Cancer* 2008; **113**: 57–64.
50 Kim MS, Lee SY, Lee TR, Cho WH, Song WS, Koh JS *et al*. Prognostic nomogram for predicting the 5-year probability of developing metastasis after neo-adjuvant chemotherapy and definitive surgery for AJCC stage II extremity osteosarcoma. *Ann Oncol* 2009; **20**: 955–960.
51 Harvin JA, Lahat G, Correa AM, Lee J, Maru D, Ajani J *et al*. Neoadjuvant chemoradiotherapy followed by surgery for esophageal adenocarcinoma: significance of microscopically positive circumferential radial margins. *J Thorac Cardiovasc Surg* 2012; **143**: 412–420.
52 Lerut T, Coosemans W, Decker G, De Leyn P, Ectors N, Fieuws S *et al*. Extracapsular lymph node involvement is a negative prognostic factor in T3 adenocarcinoma of the distal esophagus and gastroesophageal junction. *J Thorac Cardiovasc Surg* 2003; **126**: 1121–1128.
53 D'Annoville T, D'Journo XB, Loundou A, Trousse D, Dahan L, Doddoli C *et al*. Prognostic impact of the extracapsular lymph node involvement on disease-free survival according to the 7th edition of American Joint

Committee on Cancer Staging System. *Eur J Cardiothorac Surg* 2013; **44**: e207–e211.
54 Nafteux P, Lerut T, De Hertogh G, Moons J, Coosemans W, Decker G *et al*. Can extracapsular lymph node involvement be a tool to fine-tune pN1 for adenocarcinoma of the oesophagus and gastro-oesophageal junction in the Union Internationale Contre le Cancer (UICC) TNM 7th edition? *Eur J Cardiothorac Surg* 2014; **45**: 1001–1010.
55 Enlow JM, Denlinger CE, Stroud MR, Ralston JS, Reed CE. Adenocarcinoma of the esophagus with signet ring cell features portends a poor prognosis. *Ann Thorac Surg* 2013; **96**: 1927–1932.
56 Nafteux PR, Lerut TE, Villeneuve PJ, Dhaenens JM, De Hertogh G, Moons J *et al*. Signet ring cells in esophageal and gastroesophageal junction carcinomas have a more aggressive biological behavior. *Ann Surg* 2014; **260**: 1023–1029.
57 Izzo JG, Wu TT, Wu X, Ensor J, Luthra R, Pan J *et al*. Cyclin D1 guanine/adenine 870 polymorphism with altered protein expression is associated with genomic instability and aggressive clinical biology of esophageal adenocarcinoma. *J Clin Oncol* 2007; **25**: 698–707.
58 Ong CA, Shapiro J, Nason KS, Davison JM, Liu X, Ross-Innes C *et al*. Three-gene immunohistochemical panel adds to clinical staging algorithms to predict prognosis for patients with esophageal adenocarcinoma. *J Clin Oncol* 2013; **31**: 1576–1582.

Statistical nugget

Statistical models: an overview

J. Ranstam and J. A. Cook

BJS Statistical Editors

DOI: 10.1002/bjs.10240

A simple statistical model consists of an outcome and a sole explanatory (or predictor) variable. This type of model is sometimes described as bivariable as it includes only two variables. It is often used to estimate an 'unadjusted' or 'crude' effect, that is the influence of a single factor on the outcome of interest without taking account of other factors that may also influence the outcome. To produce an 'adjusted' estimate, other explanatory variables can be incorporated into the model (a multivariable model). Different models can be used for various types of outcomes (such as logistic regression for a binary outcome), although all make assumptions regarding the relationship between the variables in the model in order to estimate their effects. Less commonly it may be useful or necessary to model two or more outcomes together by assuming a joint probability distribution and constructing a model accordingly (using a multivariate model)[1].

Multivariable models have two major uses: to explain or to predict. The first purpose is to define (with allowance for multiple factors) parameter estimates. In an observational study, an estimate of the factor of interest with adjustment for other important factors is often carried out this way. It may not fully resolve the issue owing to unobserved factors and lead to a biased (although hopefully less biased) estimate. In a randomized trial, the reason for adjusting is mainly to reduce the uncertainty of the estimates (increase the precision) by adjusting for pre-specified strongly prognostic factors, accounting for randomization (stratification) factors, and adjusting for chance baseline imbalance in continuous endpoints when studying these endpoints' change from baseline.

The second purpose is to predict the outcome typically for an individual, such as recurrence of disease following treatment (or classify individual properties). Development of a multivariable model in order to predict (predictive or prognostic model) differs from those above. The best prediction model is simply the model that predicts best[2]. Predictive performance can be assessed in different ways. We will discuss the principles for model choice in each of these situations in more detail later.

References

1 Hidalgo B, Goodman M. Multivariate or multivariable regression? *Am J Public Health* 2013; **103**: 39–40.
2 Shmueli G. To explain or to predict? *Statistical Science* 2010; **25**: 289–310.