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ORIGINAL ARTICLE

Radiation dose and pathological response in oesophageal cancer patients treated with neoadjuvant chemoradiotherapy followed by surgery: a multi-institutional analysis

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ABSTRACT

Purpose: To explore whether a higher neoadjuvant radiation dose increases the probability of a pathological complete response (pCR) or pathological major response (pMR) response in oesophageal cancer patients.

Material and methods: Between 2000 and 2017, 1048 patients from four institutions were stratified according to prescribed neoadjuvant radiation doses of 36.0 Gy (13.3%), 40.0 Gy (7.4%), 41.4 Gy (20.1%), 45.0 Gy (25.5%) or 50.4 Gy (33.7%) in 1.8–2.0 Gy fractions. Endpoints were pCR (tumour regression grade (TRG) 1) and pMR (TRG 1 + 2). Multivariable binary (TRG 1 + 2 vs. TRG > 2) and ordinal (TRG 1 vs. TRG 2 vs. TRG > 2) logistic regression analyses were performed, with subgroup analyses according to histology (squamous cell carcinoma (SCC) vs. adenocarcinoma (AC)). Variables entered in the regression model along with neoadjuvant radiation dose were clinical tumour stage (cT), histology, chemotherapy regimen, induction chemotherapy and time from neoadjuvant chemoradiation to surgery.

Results: A pCR was observed in 312 patients (29.8%); in 22.7% patients with AC and in 49.6% patients with SCC. No radiation dose–response relation was observed for pCR (OR = 1.01, 95% CI: 0.98–1.05 for AC and OR = 1.03, 95% CI: 0.96–1.10 for SCC). A pMR was observed in 597 patients (57.0%); in 53.4% patients with AC and in 67.2% patients with SCC. A higher radiation dose increased the probability of achieving pMR (OR = 1.04, 95% CI: 1.02–1.05). Factors reducing this probability were advanced cT stage (reference = cT1–2; cT3: OR = 0.54, 95% CI: 0.37–0.80; cT4: OR = 0.45, 95% CI: 0.24–0.84), AC histology (reference = SCC; OR = 0.62, 95% CI: 0.44–0.88), the use of non-platinum based chemotherapy in SCC patients (OR = 0.30, 95% CI: 0.10–0.91) and platinum based chemotherapy without induction chemotherapy in patients with AC (OR = 0.56, 95% CI: 0.42–0.76). The radiation dose–response relation was confirmed in a subgroup analysis of histologic subtypes (OR = 1.02, 95% CI: 1.01–1.04 for AC and OR = 1.05, 95% CI: 1.02–1.08 for SCC).

Conclusions: Neoadjuvant radiation dose impacts pathological response in terms of pMR in oesophageal cancer patients. No radiation dose–response effect was observed for pCR. Further prospective trials are needed to investigate the dose–response relation in terms of pCR

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Introduction

Neoadjuvant chemoradiotherapy (nCRT) for locally advanced oesophageal cancer has been shown to improve locoregional control and survival compared to surgery alone in several randomised controlled trials [1–3]. These results have led to the widespread adoption of trimodality therapy as standard of care for locally advanced oesophageal cancer, consisting of preoperative chemotherapy with concurrent radiotherapy followed by oesophagectomy [4,5].

The improvement in survival after trimodality therapy is largely dependent on tumour response to nCRT, which can be assessed by histological examination of the resected oesophagus. Overall, a pathological complete response (pCR), being defined as complete absence of viable tumour cells in the resection specimen, is obtained in 16–40% of patients [1,3,6]. This wide range in pCR rates might be due to considerable heterogeneity in preoperative treatment regimens, with neoadjuvant radiation doses ranging from 36.0 Gy to

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50.4 Gy, accompanied by various chemotherapy regimens [1–3,6]. In oesophageal cancer, the use of nCRT mainly aims at pCR. However, it could be argued that patients with a complete and near-complete response might be clustered and described as pathological major response (pMR) [7]. This is a common approach for response assessment in rectal cancer patients, especially since the interval between nCRT and surgery can be heterogeneous and might impact response rates [8–12].

A possible strategy for treatment intensification could be to increase the neoadjuvant radiation dose. However, higher radiation doses to the tumour also lead to higher doses to the surrounding organs at risk (OAR) and have been shown to increase postoperative complication rates [13–18]. On the other hand, the increase in possibilities with proton therapy and the introduction of MRI guided radiation delivery, make it feasible to escalate the radiation dose without increasing the dose to OAR [19–21]. The available studies that assess whether neoadjuvant radiation dose influences tumour response rates in patients with oesophageal cancer are equivocal, and the debate regarding the optimal neoadjuvant radiation dose is still ongoing [22–25]. Therefore, the goal of the current study was to retrospectively explore the hypothesis that a higher neoadjuvant radiation dose could increase pathological tumour response rates in oesophageal cancer patients, in terms of achievement of pCR and pMR.

Material and methods

Patients

Consecutive patients with locally advanced resectable oesophageal cancer scheduled for and treated with nCRT followed by surgery at four high volume institutes between 2000 and 2017 were included. Patients were stratified according to the prescribed total neoadjuvant radiation dose of 36.0 Gy, 40.0 Gy, 41.4 Gy, 45.0 Gy and 50.4 Gy. Exclusion criteria were (1) a histologic subtype other than squamous cell carcinoma (SCC) or adenocarcinoma (AC) as based on the resection specimen and in case of a pCR based on the primary tumour biopsy, (2) the presence of distant metastases and (3) treatment with proton radiotherapy. Patients were identified from prospectively maintained databases in the following four university medical centres: University Hospitals Leuven (Belgium), University Medical Center Utrecht (the Netherlands), University of Texas MD Anderson Cancer Center (USA) and Ghent University Hospital (Belgium).

All patients underwent an endoscopy with biopsy for histological proof of malignancy and a computed tomography (CT) scan of the chest and abdomen or an ^{18}F-fluorodeoxyglucose positron emission tomography with integrated CT (^{18}F-FDG-PET/CT) for staging. Other examinations were performed according to institutional guidelines.

Treatment

Radiotherapy was delivered in fractions of 1.8 Gy or 2.0 Gy by three-dimensional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT). Delineation of the target volume was according to institutional guidelines. Typically, gross target volume (GTV) was based on endoscopy, CT and/or ^{18}F-FDG-PET/CT and expanded with a 3–4 cm margin in cranio-caudal direction and 0.5–1 cm circumferentially, respecting the anatomic boundaries. The choice of chemotherapy regimen and whether or not induction chemotherapy prior to nCRT was administered, was at the discretion of the treating multidisciplinary team. The patients receiving 36.0 Gy were treated in a single hospital and generally received platinum based chemotherapy without induction therapy. In the single hospital treating patients with 41.4 Gy, only platinum based chemotherapy and no induction therapy was given (as per CROSS trial) [3]. One hospital treated patients with both 40.0 Gy and 45.0 Gy and all patients received platinum based chemotherapy, most commonly combined with induction chemotherapy. The fourth hospital treated patients with 45.0 Gy and 50.4 Gy with either a platinum or non-platinum based chemotherapy regimen, and sometimes administered induction chemotherapy.

After nCRT, patients were scheduled for transthoracic or transhiatal surgery with two- or three-field lymphadenectomy, based on the location of the tumour and pathological lymph nodes, as well as the preference of the surgeon.

Outcome measures

Clinical and treatment-related characteristics were acquired from the prospectively collected databases at the four centres. The time from nCRT to surgery was defined as the interval in days between the last day of radiotherapy and the date of surgery. Histologic tumour regression grades (TRGs) of the primary tumour were based on histopathological evaluation of the resection specimen by dedicated gastrointestinal pathologists and grouped into three TRG groups: TRG 1 defined as Mandard 1 or 0.0% viable tumour cells (pCR), TRG 2 defined as Mandard 2 or $<$10.0% viable tumour cells and TRG $>$2 defined as Mandard $>$2 or $>$10.0% viable tumour cells [26,27]. pMR was defined as TRG 1 and 2 combined.

Overall survival was calculated based from the day of surgery to the date of all-cause death or last day of follow-up.

Statistical analysis

Summary statistics were presented as medians and interquartile range (IQR) for continuous variables, and as frequencies and percentages for categorical variables. To evaluate group differences in patient and treatment variables, the chi-square and ANOVA tests were used for categorical and continuous variables, respectively.

The relation between neoadjuvant radiation dose and pathological response was studied in a multivariable binary and ordinal logistic regression analyses. The ordinal logistic regression analysis considered three categories of the dependent variable: TRG $>$2, TRG 2 and TRG 1 (i.e., pCR). In the multivariable binary logistic regression model, the

dependent variable was categorised as TRG 1 and 2 (i.e., pMR) vs. TRG >2. Variables to be entered in the regression model along with neoadjuvant radiation dose were based on clinical relevance and literature review of potential confounders: clinical tumour stage (cT), histology, chemotherapy regimen, the use of induction chemotherapy before nCRT, and the time from nCRT to surgery. Furthermore, interactions between histology and (induction) chemotherapy were added to the models when appropriate. Pre-specified subgroup analyses by histology were performed. Patients with missing outcome or covariables were excluded from the analyses.

The Kaplan–Meier method was used to estimate overall survival of pCR and pMR in the entire patient cohort and according to histology.

All analyses were performed with SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patients

A total of 1102 patients were retrieved from the databases. Fifty-four patients (45 patients with AC and nine patients with SCC) with a missing endpoint or covariable were excluded, resulting in 1048 patients eligible for analyses (Supplementary Material 1). Patients received either 36.0 Gy (139, 13.3%), 40.0 Gy (78, 7.4%), 41.4 Gy (211, 20.1%), 45.0 Gy (267, 25.5%) or 50.4 Gy (353, 33.7%). Patient, tumour and treatment-related characteristics of the patient cohort are presented in Table 1. The majority of patients were male (837, 79.9%) and the median age was 62 years (IQR 55–68 years). The predominant histologic tumour type was AC (774, 73.9%) and cT3 was the most common tumour stage (857, 81.8%). Most patients had positive lymph nodes upon clinical staging (796, 76.0%). The patients treated with 36.0 Gy received platinum based chemotherapy (except one) without induction therapy (except one). In one hospital treating patients with 45.0 Gy and 50.4 Gy, a non-platinum based chemotherapy regimen was administered in half of the cases and induction chemotherapy was given in 38.3% of all patients.

Pathologic complete response

A pCR was demonstrated in 312 patients (29.8%), of which 176 of 774 patients (22.7%) with AC and 136 of 274 patients (49.6%) with SCC. A dose–response diagram for the endpoint TRG 1 (pCR) vs. TRG 2 vs. TRG >2 is presented in Figure 1.

Multivariable ordinal logistic regression analysis with TRG >2, TRG 2 and TRG 1 as outcome categories demonstrated no significant impact of total neoadjuvant radiation dose for both histologic subtypes (per additional Gy: OR 1.01, 95% CI 0.98–1.05, $p = .403$ for AC and OR 1.03, 95% CI 0.96–1.10, $p = .402$ for SCC) (Table 2). In the patients with AC, advanced tumour stage (with cT1–2 as reference; cT3–4: OR 0.53, 95% CI 0.36–0.78, $p = .002$) and the use of platinum based chemotherapy without induction chemotherapy (OR 0.56, 95% CI 0.41–0.77, $p < .001$) reduced the odds of a pathological response. For patients with SCC, only an advanced tumour stage reduced the odds of a pathological response (with cT1–2 as reference; cT3–4: OR 0.45, 95% CI 0.12–1.11, $p = .030$).

Pathologic major response

A pMR was obtained in 597 of 1048 patients (57.0%). In binary multivariable logistic regression analysis with pMR as outcome, the total neoadjuvant radiation dose increased the odds of pMR (per additional Gy: OR 1.04, 95% CI 1.02–1.05, $p < .001$). Factors that reduced these odds were a higher tumour stage (with cT1–2 as reference; cT3: OR 0.54, 95% CI 0.37–0.80, $p = .002$ and cT4: OR 0.45, 95% CI 0.24–0.84, $p = .013$) as well as AC histology (OR 0.62, 95% CI 0.44–0.88, $p = .008$). The use of non-platinum based chemotherapy in patients with SCC decreased the odds of pMR (OR 0.30, 95%

Table 1. Baseline characteristics of the study population.

		Total	36.0 Gy	40.0 Gy	41.4 Gy	45.0 Gy	50.4 Gy	*p* Value
Patients	*n* (%)	1048 (100.0)	139 (13.3)	78 (7.4)	211 (20.1)	267 (25.5)	353 (33.7)	
Age at diagnosis, years	Median (IQR)	62 (55–68)	62 (55–69)	60 (53–66)	67 (60–71)	62 (55–69)	60 (52–65)	<.001
Sex	Male (*n* (%))	837 (79.9)	112 (80.6)	58 (74.4)	160 (75.8)	196 (73.4)	311 (88.1)	<.001
	Female (*n* (%))	211 (20.1)	27 (19.4)	20 (25.6)	51 (24.2)	71 (26.6)	42 (11.9)	
Chemotherapy regimen	Platinum based (*n* (%))	852 (81.3)	138 (99.3)	78 (100.0)	211 (100.0)	246 (92.1)	179 (50.7)	<.001
	Non-platinum based (*n* (%))	196 (18.7)	1 (0.7)	0 (0.0)	0 (0.0)	21 (7.9)	174 (49.3)	
Induction chemotherapy	Yes (*n* (%))	420 (40.1)	1 (0.7)	61 (78.2)	0 (0.0)	235 (88.0)	123 (34.8)	<.001
	No (*n* (%))	628 (59.9)	138 (99.3)	17 (21.8)	211 (100.0)	32 (12.0)	230 (65.2)	
Days end radiation until surgery	Median (IQR)	53 (44–64)	34 (29–38)	55 (47–64)	62 (50–75)	55 (47–64)	57 (47–78)	<.001
cT	1 (*n* (%))	8 (0.8)	2 (1.4)	0 (0.0)	3 (1.4)	1 (0.4)	2 (0.6)	<.001
	2 (*n* (%))	126 (12.0)	15 (10.8)	6 (7.7)	36 (17.1)	31 (11.6)	38 (10.8)	
	3 (*n* (%))	857 (81.8)	117 (84.2)	46 (59.0)	169 (80.1)	218 (81.6)	307 (87.0)	
	4 (*n* (%))	57 (5.4)	5 (3.6)	26 (33.3)	3 (1.4)	17 (6.4)	6 (1.7)	
cN	0 (*n* (%))	244 (23.3)	20 (14.4)	4 (5.1)	59 (28.0)	37 (13.9)	124 (35.1)	<.001
	+ (*n* (%))	796 (76.0)	113 (81.3)	73 (93.6)	152 (72.0)	230 (86.1)	228 (64.6)	
	x (*n* (%))	8 (0.8)	6 (4.3)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)	
Histology	SCC (*n* (%))	274 (26.1)	52 (37.4)	44 (56.4)	66 (31.3)	81 (30.3)	31 (8.8)	<.001
	AC (*n* (%))	774 (73.9)	87 (62.6)	34 (43.6)	145 (68.7)	186 (69.7)	322 (91.2)	
TRG	1 (*n* (%))	312 (29.8)	37 (26.6)	26 (33.3)	63 (29.9)	89 (33.3)	97 (27.5)	
	2 (*n* (%))	285 (27.2)	35 (25.2)	20 (25.6)	45 (21.3)	83 (31.1)	102 (28.9)	
	>2 (*n* (%))	451 (43.0)	67 (48.2)	32 (41.0)	103 (48.8)	95 (35.6)	154 (43.6)	

n: number; IQR: interquartile range; cT: clinical tumour stage; cN: clinical nodal stage; SCC: squamous cell carcinoma; AC: adenocarcinoma; TRG: tumour regression grade.

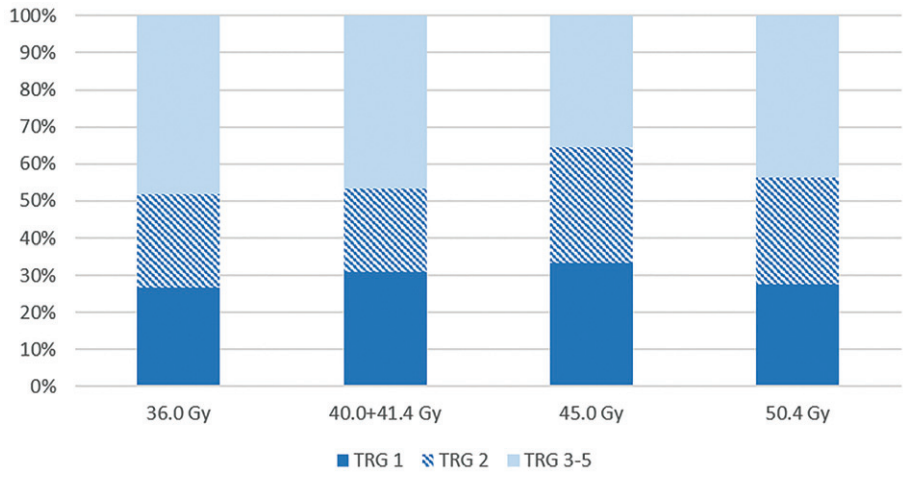

Figure 1. Dose–response diagram for the endpoint TRG 1 vs. TRG 2 vs. TRG >2 in the entire patient cohort. TRG: tumour regression grade. To facilitate the visualisation of the diagrams (in relative numbers), the 40.0 Gy and 41.1 Gy dose levels were combined.

Table 2. Multivariable ordinal logistic regression analysis with three pathological response groups as outcome variable (TRG >2, TRG 2 and TRG 1 (pCR)), according to histologic subgroups.

	OR (95% CI)	*p* Value
774 patients with adenocarcinoma		
Total neoadjuvant radiation dose per Gy	1.01 (0.98–1.05)	.403
Tumour stage (cT1–2 as reference)[a]		
cT3–4	0.53 (0.36–0.78)	**.002**
Platinum based chemotherapy without induction chemotherapy	0.56 (0.41–0.77)	**<.001**
Days between neoadjuvant chemoradiotherapy and surgery	1.00 (0.99–1.01)	.812
274 patients with squamous cell carcinoma		
Total neoadjuvant radiation dose per Gy	1.03 (0.96–1.10)	.402
Tumour stage (cT1–2 as reference)[a]		
cT3–4	0.45 (0.12–1.11)	**.030**
Non-platinum based chemotherapy	0.36 (0.41–0.77)	.076
Days between neoadjuvant chemoradiotherapy and surgery	1.00 (0.99–1.01)	.878

TRG: tumour regression grade; pCR: pathological complete response; OR: odds ratio; 95% CI: 95% confidence interval; cT: clinical tumour stage.
Significant *p* values (<.050) are highlighted in bold.
The Test of Parallel Lines had a *p* value of .051 (degrees of freedom (df) = 4, adenocarcinoma) and .386 (df = 4, squamous cell carcinoma), respectively.
[a]Clinical tumour stages were combined for these subgroup analyses because of small patient numbers per stage.

CI: 0.10–0.91, $p = .034$). The use of platinum based chemotherapy without induction chemotherapy in patients with AC had a negative effect on pMR (OR 0.56, 95% CI 0.42–0.76, $p < .001$) (Table 3).

Subgroup analyses for pathologic major response according to histology

In patients with AC, a pMR was achieved in 413 of 774 patients (53.4%). In binary multivariable logistic regression analysis with pMR as outcome, the total neoadjuvant radiation dose increased the odds of pMR (per additional Gy: OR 1.02, 95% CI 1.01–1.04, $p < .001$). Factors reducing the odds were advanced tumour stage (with cT1–2 as reference; cT3: OR 0.59, 95% CI 0.38–0.91, $p = .016$ and cT4: OR 0.56, 95% CI 0.23–1.36, $p = .199$) and the use of platinum based chemotherapy without induction chemotherapy (OR 0.54, 95% CI 0.41–0.72, $p < .001$) (Table 3).

For SCC, 184 of 274 patients (67.2%) achieved a pMR. In multivariable binary logistic regression analysis with pMR as outcome, the total neoadjuvant radiation dose increased the odds of pMR (per additional Gy: OR 1.05, 95% CI 1.02–1.08, $p = .001$). Factors that reduced these odds were higher tumour stage (with cT1–2 as reference; cT3: OR 0.32, 95% CI 0.12–0.82, $p = .018$ and cT4: OR 0.23, 95% CI 0.07–0.71, $p = .011$) and the use of non-platinum based chemotherapy (OR 0.27, 95% CI 0.09–0.83, $p = .022$).

Survival analysis

Median follow-up time of the patients was 25.1 months (IQR 11.0–54.7 months).

The median OS of patients with a pCR, TRG 2 and TRG >2 was 78 months, 46 months and 28 months, respectively (Supplementary Material 2). For patients with an AC, the median OS was 90 months for pCR, 50 months for TRG 2 and 30 months TRG >2. For patients with an SCC, the median OS was 67 months for pCR, 38 months for TRG 2 and 16 months TRG >2 (Supplementary Material 2).

The median OS of patients with a pMR and TRG >2 was 61 months and 28 months, respectively (Figure 2). For patients with an AC, the median OS was 64 months for pMR

Table 3. Multivariable logistic regression analysis with pathological major response (pMR) as outcome variable in the entire patient cohort and according to histologic subgroups.

	OR (95% CI)	p Value
1048 patients		
Total neoadjuvant radiation dose per Gy	1.04 (1.02–1.05)	**<.001**
Histology (squamous cell carcinoma as reference)	0.62 (0.44–0.88)	**.008**
Tumour stage (cT1–2 as reference)[a]		
cT3	0.54 (0.37–0.80)	**.002**
cT4	0.45 (0.24–0.84)	**.013**
Interaction between adenocarcinoma and platinum based chemotherapy without induction chemotherapy	0.56 (0.42–0.76)	**<.001**
Interaction between squamous cell carcinoma and non-platinum based chemotherapy	0.30 (0.10–0.91)	**.034**
Days between neoadjuvant chemoradiotherapy and surgery	1.00 (0.99–1.00)	.241
774 patients with adenocarcinoma		
Total neoadjuvant radiation dose per Gy	1.02 (1.01–1.04)	**<.001**
Tumour stage (cT1–2 as reference)[a]		
cT3	0.59 (0.38–0.91)	**.016**
cT4	0.56 (0.23–1.36)	.199
Platinum based chemotherapy without induction chemotherapy	0.54 (0.41–0.72)	**<.001**
Days between neoadjuvant chemoradiotherapy and surgery	1.00 (0.99–1.00)	.291
274 patients with squamous cell carcinoma		
Total neoadjuvant radiation dose per Gy	1.05 (1.02–1.08)	**.001**
Tumour stage (cT1–2 as reference)[a]		
cT3	0.32 (0.12–0.82)	**.018**
cT4	0.23 (0.07–0.71)	**.011**
Non-platinum based chemotherapy	0.27 (0.09–0.83)	**.022**
Days between neoadjuvant chemoradiotherapy and surgery	1.00 (0.98–1.01)	.674

pMR: pathological major response; OR: odds ratio; 95% CI: 95% confidence interval; cT: clinical tumour stage.
Significant *p* values (<.050) are highlighted in bold.
The Hosmer–Lemeshow goodness of fit had a *p* value of 0.399 (degrees of freedom (df)=8, entire patient cohort), 0.754 (df = 8, adenocarcinoma) and 0.276 (df = 8, squamous cell carcinoma), respectively.
[a]cT1 and cT2 were combined as a reference category, since only few patients had a cT1 stage.

and 30 months TRG >2. For patients with an SCC patients, the median OS was 55 months for pMR and 16 months TRG >2 (Figure 2).

Discussion

In this study, we analysed the pathological response rate after nCRT followed by surgery in 1048 patients with oesophageal cancer from four high volume institutes. The balance between the pathological response and the toxicity of neoadjuvant therapy emphasises the need to explore a dose–response relationship, especially in the era of an increasing use of a wait-and-see policy in clinical complete responders. Some evidence of a dose–response relation has been described in observational studies [22,25]. To our knowledge, no randomised controlled trials have been performed comparing different neoadjuvant radiotherapy schedules for patients with oesophageal cancer. Our study did not observe a dose–response relation for pCR (TRG 1) in multivariable ordinal regression analyses. However, a dose–response relation was observed for radiation dose and pMR (TRG 1 + 2), where the neoadjuvant radiation dose, besides the tumour stage, histology, induction chemotherapy and the chemotherapy regimen, increased the odds of a pMR. As the cohort of patients with SCC was rather small compared to that of the patients with AC, especially in the subgroup of non-platinum based chemotherapy and in the group of patients receiving 50.4 Gy, the effect of dose in patients with SCC should be interpreted with caution.

Next to the neoadjuvant radiation dose, the impact of the concurrent chemotherapy regimen and the use of induction chemotherapy was studied. A non-platinum based chemotherapy was less effective to achieve a pMR in patients with SCC. When induction chemotherapy was administered in patients with AC, there was an improvement in pMR only when platinum based chemotherapy was used concomitantly. In literature, limited data are available on the use of non-platinum based chemotherapy and the pathological response rate in patients with SCC and AC separately in the preoperative setting in oesophageal cancer patients [28,29]. The observed differences in chemo- and radiotherapy sensitivity underline the necessity for researching individualised treatment regimens for both histologic subgroups.

Next to pCR, pMR was chosen as secondary outcome variable for several reasons. First, the interval between the last day of radiotherapy and the surgery might affect the degree of pathological response, i.e., a shorter interval between nCRT and surgery might underestimate the presence of a pathological response [30]. To eliminate this bias, the interval between nCRT and surgery was taken into account in the multivariable analyses, and pathological complete and near-complete responders were grouped as patients with pMR in a secondary analysis as well. Second, the benefit in overall survival and progression free survival has been suggested to be comparable between patients with a pCR and those with a low percentage of residual tumour cells in a meta-analysis [8]. Lastly, a similar strategy has been applied in other cancer types, such as rectal cancer, where both clinical complete and near-complete responders are considered eligible for an organ-preservation strategy [9].

In our study, reaching a pMR or pCR, compared to TRG >2, was as expected associated with a survival advantage, both in the entire patient cohort as in the subgroups according to histology [8,31]. Despite the large patient cohort, we

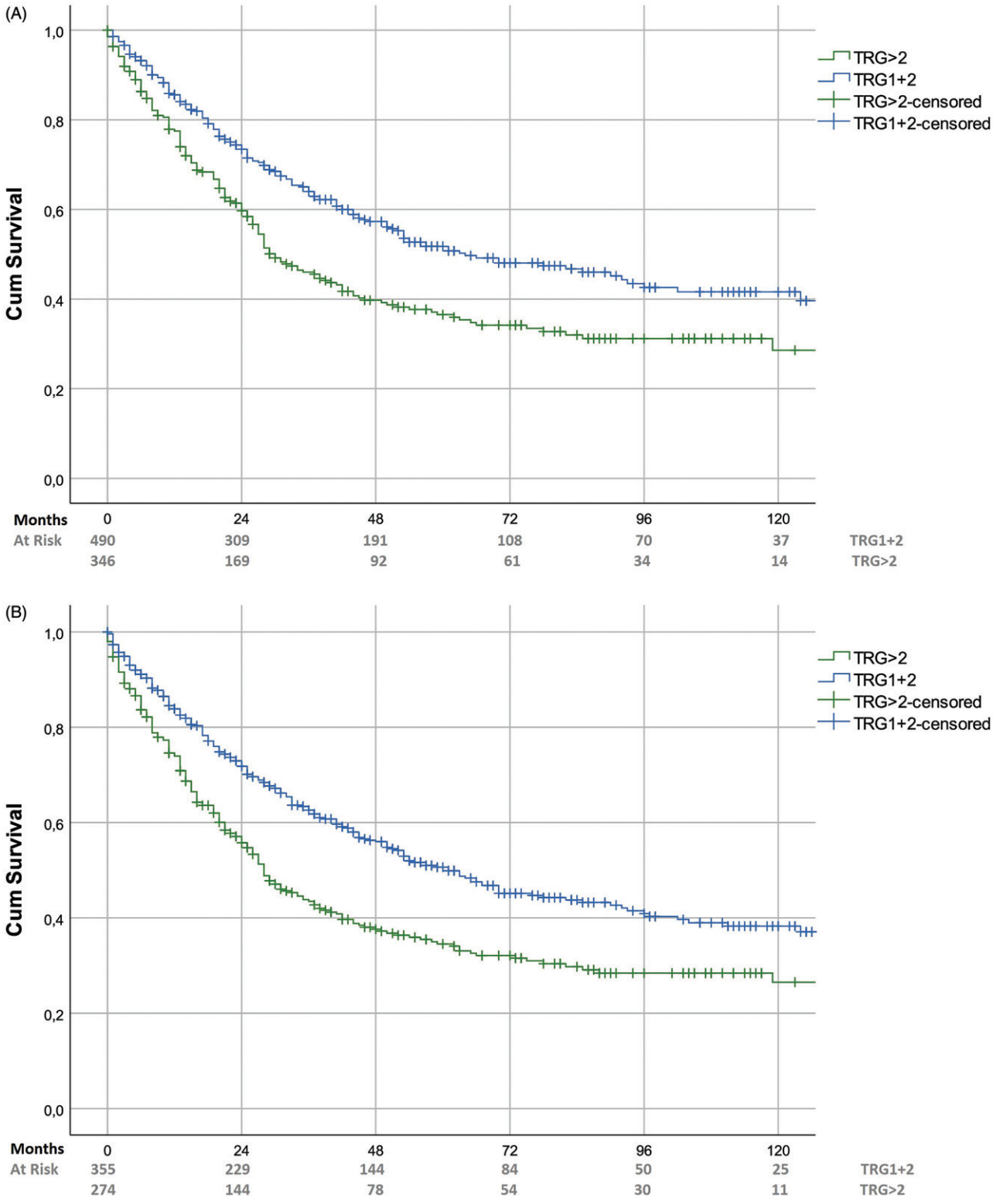

Figure 2. Overall survival curves of TRG 1 + 2 (pMR) vs. TRG >2 in the entire patient cohort (A) and according to histologic subgroups (B). pMR: pathological major response; TRG: tumour regression grade.

acknowledge that these analyses were subject to an unbalanced distribution of confounders, related to clinical and treatment-related variables.

Potential limitations of this study include its retrospective nature. Additionally, the TRG was evaluated by centre-specific pathologists and only evaluated the regression grade of the primary tumour and not of the lymph nodes. As a consequence, persistent disease only at the nodal level was possible [32–34]. Since the lack of adequate TRG systems for nodes after preoperative treatment and the relatively low percentage of patients in our study with an ypT0N+, the current study focussed on the primary tumour. However, in

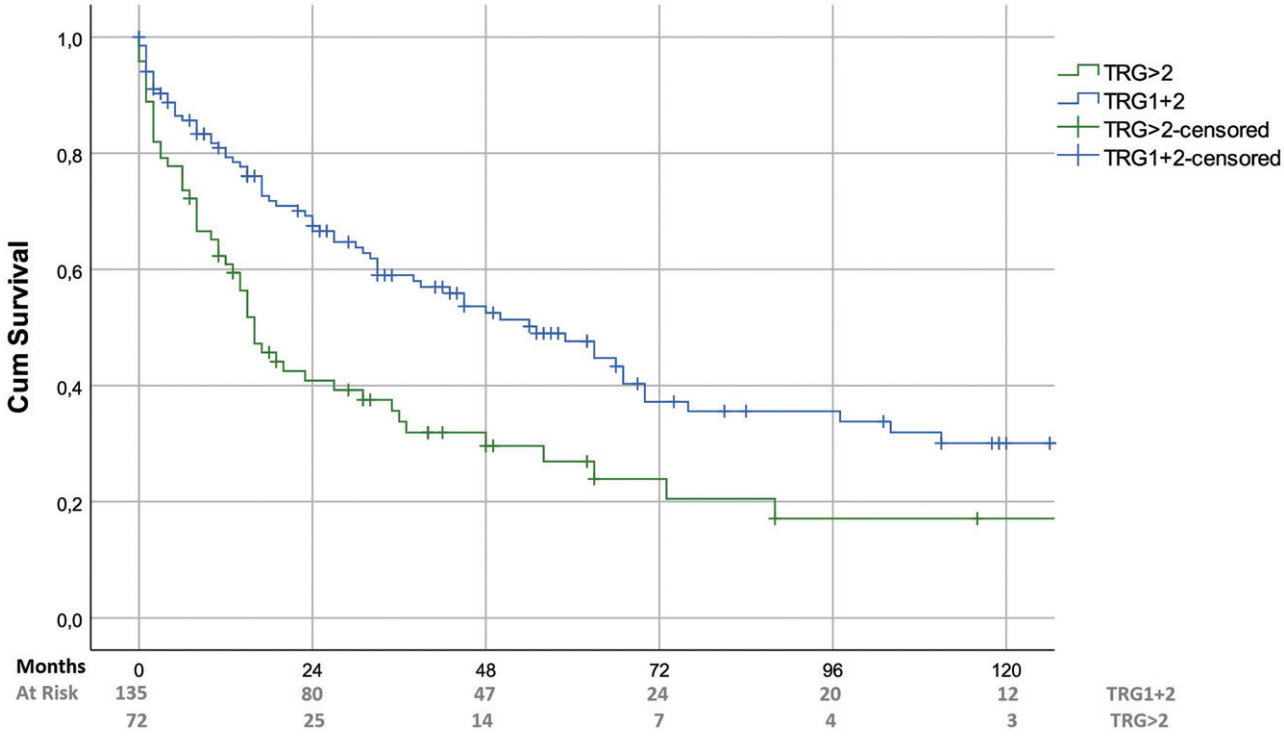

Figure 2. Continued.

order to investigate the effect of increased neoadjuvant radiation dose on survival, the response of the primary tumour should be combined with the pathological nodal stage, since the latter is one of the most important determinants of overall survival after nCRT followed by surgery [8,35,36]. Another limitation involves that all patients scheduled for and actually treated with nCRT followed by surgery (i.e., preoperative intent) were included in the analysis. As such, there might have been a selection bias by excluding patients who started nCRT but did not proceed to surgery, e.g., patients with a clinical complete response in whom an active surveillance strategy was applied. On the other hand, in a few patients surgery was delayed, due to prolonged treatment recovery from nCRT and observation. Additionally, toxicity data were not available and further studies are warranted to investigate the influence of nCRT on toxicity and postoperative complications. Lastly, we acknowledge that the treatment regimen, i.e., radiation dose and concurrent chemotherapy regimen, was directly linked to the centre, which might have resulted in residual confounding. Despite the aforementioned limitations, major strengths of this study include that this is a large multi-centre study, based on high-quality prospectively collected data. In contrast to previous studies, information on the concurrent chemotherapy regimen and on the use of induction chemotherapy was available, which is important in analysing pathological response rates.

In conclusion, this study demonstrated that the total neoadjuvant radiation dose had an impact on pathological response in terms of pMR in patients with oesophageal cancer. However, no radiation dose–response effect was observed for pCR. Further prospective trials are needed to investigate the dose–response relation in terms of pCR.

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Disclosure statement

The authors report no conflicts of interest.

References

[1] Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26:1086–1092.

[2] Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12:681–692.

[3] van Hagen P, Hulshof M, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074–2084.

[4] Lagergren J, Smyth E, Cunningham D, et al. Oesophageal cancer. Lancet. 2017;390:2383–2396.

[5] Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v50–v57.

[6] Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol. 2005;6:659–668.

[7] Depypere L, Moons J, Lerut T, et al. Neoadjuvant chemoradiation treatment followed by surgery for esophageal cancer: there is

much more than the Mandard tumor regression score. Acta Chir Belg. 2016;116:149–155.
[8] Tomasello G, Petrelli F, Ghidini M, et al. Tumor regression grade and survival after neoadjuvant treatment in gastro-esophageal cancer: a meta-analysis of 17 published studies. Eur J Surg Oncol. 2017;43:1607–1616.
[9] Hupkens BJP, Maas M, Martens MH, et al. Organ preservation in rectal cancer after chemoradiation: should we extend the observation period in patients with a clinical near-complete response? Ann Surg Oncol. 2018;25:197–203.
[10] Lee A, Wong AT, Schwartz D, et al. Is there a benefit to prolonging the interval between neoadjuvant chemoradiation and esophagectomy in esophageal cancer? Ann Thorac Surg. 2016; 102:433–438.
[11] Haisley KR, Laird AE, Nabavizadeh N, et al. Association of intervals between neoadjuvant chemoradiation and surgical resection with pathologic complete response and survival in patients with esophageal cancer. JAMA Surg. 2016;151:e162743.
[12] Tie H, He F, Shen J, et al. Prolonged interval between neoadjuvant chemoradiotherapy and esophagectomy does not benefit the outcome in esophageal cancer: a systematic review and meta-analysis. Dis Esophagus. 2018;31:1–9.
[13] Vande Walle C, Ceelen WP, Boterberg T, et al. Anastomotic complications after Ivor Lewis esophagectomy in patients treated with neoadjuvant chemoradiation are related to radiation dose to the gastric fundus. Int J Radiat Oncol Biol Phys. 2012;82: e513–e519.
[14] Hatakenaka M, Yonezawa M, Nonoshita T, et al. Acute cardiac impairment associated with concurrent chemoradiotherapy for esophageal cancer: magnetic resonance evaluation. Int J Radiat Oncol Biol Phys. 2012;83:e67–e73.
[15] Beukema JC, van Luijk P, Widder J, et al. Is cardiac toxicity a relevant issue in the radiation treatment of esophageal cancer? Radiother Oncol. 2015;114:85–90.
[16] Lee HK, Vaporciyan AA, Cox JD, et al. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose–volume histogram parameters. Int J Radiat Oncol Biol Phys. 2003;57:1317–1322.
[17] Wang SL, Liao Z, Vaporciyan AA, et al. Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys. 2006;64:692–699.
[18] Tucker SL, Liu HH, Wang S, et al. Dose–volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys. 2006;66: 754–761.
[19] Lagendijk JJW, Raaymakers BW, Raaijmakers AJE, et al. MRI/linac integration. Radiother Oncol. 2008;86:25–29.
[20] Welsh J, Gomez D, Palmer MB, et al. Intensity-modulated proton therapy further reduces normal tissue exposure during definitive therapy for locally advanced distal esophageal tumors: a dosimetric study. Int J Radiat Oncol Biol Phys. 2011;81:1336–1342.
[21] Lin SH, Merrell KW, Shen J, et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer. Radiother Oncol. 2017;123:376–381.
[22] Geh JI, Bond SJ, Bentzen SM, et al. Systematic overview of preoperative (neoadjuvant) chemoradiotherapy trials in oesophageal cancer: evidence of a radiation and chemotherapy dose response. Radiother Oncol. 2006;78:236–244.
[23] Venkat PS, Shridhar R, Naghavi AO, et al. Dose escalated neoadjuvant chemoradiotherapy with dose-painting intensity-modulated radiation therapy and improved pathologic complete response in locally advanced esophageal cancer. Dis Esophagus. 2017;30:1–9.
[24] Ji KSY, Thomas SM, Roman SA, et al. Low- vs. high-dose neoadjuvant radiation in trimodality treatment of locally advanced esophageal cancer. J Gastrointest Surg. 2019;23:885–894.
[25] Semenkovich TR, Samson PP, Hudson JL, et al. Induction radiation therapy for esophageal cancer: does dose affect outcomes? Ann Thorac Surg. 2019;107:903–911.
[26] Mandard A, Dalibard F, Mandard J, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994;73:2680–2686.
[27] Becker K, Mueller JD, Schulmacher C, et al. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer. 2003;98:1521–1530.
[28] Ajani JA, Correa AM, Walsh GL, et al. Trimodality therapy without a platinum compound for localized carcinoma of the esophagus and gastroesophageal junction. Cancer. 2010;116:1656–1663.
[29] Kushida T, Nohara S, Yoshino K, et al. Utility of weekly docetaxel combined with preoperative radiotherapy for locally advanced esophageal cancer from pathological analysis. Dis Esophagus. 2014;27:368–373.
[30] Shapiro J, van Hagen P, Lingsma HF, et al. Prolonged time to surgery after neoadjuvant chemoradiotherapy increases histopathological response without affecting survival in patients with esophageal or junctional cancer. Ann Surg. 2014;260:807–814.
[31] Meredith KL, Weber JM, Turaga KK, et al. Pathologic response after neoadjuvant therapy is the major determinant of survival in patients with esophageal cancer. Ann Surg Oncol. 2010;17: 1159–1167.
[32] Lv HW, Li Y, Zhou MH, et al. Remnant lymph node metastases after neoadjuvant therapy and surgery in patients with pathologic T0 esophageal carcinoma impact on prognosis: a systematic review and meta-analysis. Medicine. 2017;96:1–6.
[33] Depypere L, Vervloet G, Lerut T, et al. ypT0N+: the unusual patient with pathological complete tumor response but with residual lymph node disease after neoadjuvant chemoradiation for esophageal cancer, what's up? J Thorac Dis. 2018;10: 2771–2778.
[34] Schurink B, Seesing MFJ, Goense L, et al. ypT0N + status in oesophageal cancer patients: location of residual metastatic lymph nodes with regards to the neoadjuvant radiation field. Eur J Surg Oncol. 2019;45:454–459.
[35] Hölscher AH, Drebber U, Schmidt H, et al. Prognostic classification of histopathologic response to neoadjuvant therapy in esophageal adenocarcinoma. Ann Surg. 2014;260:779–785.
[36] Reynolds JV, Muldoon C, Hollywood D, et al. Long-term outcomes following neoadjuvant chemoradiotherapy for esophageal cancer. Ann Surg. 2007;245:707–716.