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ORIGINAL ARTICLE

Oncological outcomes of standard versus prolonged time to surgery after neoadjuvant chemoradiotherapy for oesophageal cancer in the multicentre, randomised, controlled NeoRes II trial

K. Nilsson[1,2], F. Klevebro[1,2], B. Sunde[1,2], I. Rouvelas[1,2], M. Lindblad[1,2], E. Szabo[3], I. Halldestam[4], U. Smedh[5], B. Wallner[6], J. Johansson[7], G. Johnsen[8], E. K. Aahlin[9], H.-O. Johannessen[10], G. Alexandersson von Döbeln[2,11], G. O. Hjortland[12], N. Wang[13], Y. Shang[14], D. Borg[15], A. Quaas[16], I. Bartella[17], C. Bruns[17], W. Schröder[17] & M. Nilsson[1,2]*

[1]Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm; [2]Division of Surgery and Oncology, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm; [3]Department of Surgery, Faculty of Medicine and Health, Örebro University Hospital, Örebro; [4]University Hospital of Linköping, Linköping; [5]Department of Surgery, Sahlgrenska University Hospital, Gothenburg; [6]Department of Surgical and Perioperative Sciences, Surgery, Umeå University, Umeå; [7]Department of Surgery, Skåne University Hospital, Lund, Sweden; [8]Department of Gastrointestinal Surgery, St. Olav's Hospital, Trondheim University Hospital, Trondheim; [9]Department of GI and HPB Surgery, University Hospital of Northern Norway, Tromsø; [10]Department of Gastrointestinal Surgery, Oslo University Hospital, Oslo, Norway; [11]Medical Unit of Head, Neck, Lung and Skin Cancer, Karolinska University Hospital, Stockholm, Sweden; [12]Department of Oncology, Oslo University Hospital, Oslo, Norway; [13]Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm; [14]Department of Medicine Huddinge, Karolinska Institutet, Stockholm;[15]Department of Oncology, Skåne University Hospital, Lund, Sweden; [16]Institute of Pathology, University of Cologne, Cologne; [17]Department of General, Visceral, Cancer and Transplantation Surgery, University Hospital of Cologne, Cologne, Germany

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Background: The optimal time to surgery (TTS) after neoadjuvant chemoradiotherapy (nCRT) for oesophageal cancer is unknown and has traditionally been 4-6 weeks in clinical practice. Observational studies have suggested better outcomes, especially in terms of histological response, after prolonged delay of up to 3 months after nCRT. The NeoRes II trial is the first randomised trial to compare standard to prolonged TTS after nCRT for oesophageal cancer.

Patients and methods: Patients with resectable, locally advanced oesophageal cancer were randomly assigned to standard delay of surgery of 4-6 weeks or prolonged delay of 10-12 weeks after nCRT. The primary endpoint was complete histological response of the primary tumour in patients with adenocarcinoma (AC). Secondary endpoints included histological tumour response, resection margins, overall and progression-free survival in all patients and stratified by histologic type.

Results: Between February 2015 and March 2019, 249 patients from 10 participating centres in Sweden, Norway and Germany were randomised: 125 to standard and 124 to prolonged TTS. There was no significant difference in complete histological response between AC patients allocated to standard (21%) compared to prolonged (26%) TTS ($P = 0.429$). Tumour regression, resection margins and number of resected lymph nodes, total and metastatic, did not differ between the allocated interventions. The first quartile overall survival in patients allocated to standard TTS was 26.5 months compared to 14.2 months after prolonged TTS ($P = 0.003$) and the overall risk of death during follow-up was 35% higher after prolonged delay (hazard ratio 1.35, 95% confidence interval 0.94-1.95, $P = 0.107$).

Conclusion: Prolonged TTS did not improve histological complete response or other pathological endpoints, while there was a strong trend towards worse survival, suggesting caution in routinely delaying surgery for >6 weeks after nCRT.

Key words: oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, neoadjuvant chemoradiotherapy, standard time, prolonged time, surgery

INTRODUCTION

The timing of curative-intent surgery after neoadjuvant chemoradiotherapy (nCRT) for oesophageal cancer is a matter of controversy, for which no high-grade evidence is available. The recently published ESMO Clinical Practice Guidelines for Oesophageal Cancer recommend two alternative adjunct therapy options: perioperative chemotherapy using the FLOT regimen for adenocarcinoma (AC) or CROSS-type nCRT comprising weekly paclitaxel and

*Correspondence to: Prof. Magnus Nilsson, Department of Upper Abdominal Diseases, Karolinska University Hospital and Division of Surgery and Oncology, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Hälsovägen 13, C1-77, 141 57 Stockholm, Sweden. Tel: +46-736402021

E-mail: magnus.nilsson@ki.se (M. Nilsson).

carboplatin with concomitant 41.4 Gy of radiotherapy for both AC and squamous cell carcinoma (SCC).[1] So far, randomised studies have not shown any difference in survival between nCRT and chemotherapy alone[2,3] and recently the CheckMate 577 trial established adjuvant nivolumab as standard practice following nCRT with residual tumour in the specimen, further promoting nCRT as standard of care in curative-intent treatment of oesophageal cancer.[4]

The optimal time interval between completed nCRT and surgical resection is not known. Approximately 6 weeks' delay from nCRT to surgery was implemented when nCRT was first introduced in the 1960s. This time span was found adequate for patients to recover and to allow for local inflammation to subside without allowing the tumour to progress before surgery.[5] In the last decades, the most commonly recommended interval between nCRT and surgery for patients with oesophageal cancer has been 4-6 weeks, both in clinical practice and in most published trials, including the CROSS trial.[3,6-8]

In an observational study based on the CROSS trial chemoradiotherapy arm cohort, a gradually increasing probability of histological complete response was reported with increasing delay of surgery between 6.5 and 12 weeks after completed nCRT.[9] Several retrospective observational studies have assessed the impact of the time to surgery (TTS) after nCRT on histological response and survival, with varying results.[10-27] In the last years, clinical practice has gradually changed towards increased TTS after nCRT, with close to half of the patients being operated after >6 weeks' delay.[25] To date, no other randomised trial has compared standard versus prolonged TTS after nCRT.

The aim of this study was to evaluate prolonged TTS of 10-12 weeks after nCRT compared to the standard time of 4-6 weeks regarding oncological endpoints, including histological tumour response defined as tumour regression of the primary tumour, metastatic lymph node status, tumour-free resection margins and survival. A prespecified hypothesis was that prolonged TTS after nCRT would lead to increased histological tumour regression, which in turn could lead to fewer locoregional recurrences and improved survival. In a previous publication we reported that there was no significant difference between standard and prolonged TTS regarding post-operative morbidity or mortality.[28]

PATIENTS AND METHODS

Study design and participants

The NeoRes II trial is a two-armed, open-label, randomised, controlled, multicentre trial including patients with AC or SCC of the oesophagus or oesophago-gastric junction (Siewert type I or II), comparing standard TTS of 4-6 weeks to prolonged TTS of 10-12 weeks, following completion of nCRT. Patients were enrolled at 10 European university hospitals, 6 in Sweden, 3 in Norway and 1 in Germany.

Eligible patients were aged 80 years or less, had baseline clinical stage T1N1-3M0 or T2-4aN0-3M0 and had completed CROSS-type nCRT comprising five cycles of carboplatin, area under the curve 2 mg/ml per minute and paclitaxel 50 mg/m^2 of body surface area and a total concurrent radiation dose of 41.4 Gy in 23 fractions of 1.8 Gy starting on the first day of the first chemotherapy cycle. A minimum of 80% (4 out of 5 cycles) of the chemotherapy and 90% (21 out of 23 fractions = 37.8 Gy) of the total radiation dose were required. Furthermore, Eastern Cooperative Oncology Group performance status 0-1 before neoadjuvant treatment was required and the patients had to be considered physiologically and technically operable after nCRT.

Exclusion criteria were tumour location in the upper third of the oesophagus, endoscopically defined as upper tumour border 22 cm or less from the incisors, diagnosis of concurrent malignancy within 5 years from oesophageal cancer diagnosis (except for non-melanoma skin cancer), ongoing antitumoural treatment, predicted inability to comply with the protocol and finally local or distant disease progression upon restaging after terminated chemoradiotherapy.

Clinical staging before initiation of treatment was carried out according to the routines of each study site and comprised at least endoscopy with multiple biopsies and computed tomography (CT). [^{18}F]2-fluoro-2-deoxy-D-glucose—positron emission tomography—CT (FDG—PET—CT) was recommended and used at all study sites but one. Further evaluation with endoscopic ultrasonography, endobronchial ultrasonography and staging laparoscopy was carried out in accordance with each study site's routines. Restaging after completed nCRT was carried out within 10 days after termination of treatment, using CT or FDG—PET—CT, by investigators' choice.

The protocol (Supplementary Data, available at https://doi.org/10.1016/j.annonc.2023.08.010) was approved by the ethical review committees at each study site. The study was registered in ClinicalTrials.gov, registration number NCT02415101.

Randomisation and blinding

Patients were enrolled within 2 weeks after completed nCRT and randomly assigned 1 : 1 to each intervention group. Stratification factors were study site, histology and tumour location into (i) SCC, (ii) oesophageal and gastro-oesophageal junction Siewert type I AC and (iii) gastro-oesophageal junction Siewert type II AC. Randomisation was done electronically with computer-generated randomisation lists for each stratum with a block size of four. Allocation was open label, without blinding.

Procedures

For patients allocated to standard TTS, surgical resection was planned 4-6 weeks after termination of nCRT. For those allocated to prolonged TTS, resection was planned 10-12 weeks after nCRT.

In the patients allocated to prolonged TTS, additional endoscopic evaluation and assessment of dysphagia was carried out 4-6 weeks after termination of nCRT, to detect signs of local tumour progression. If tumour progression

was suspected endoscopically, or if there was any increase in dysphagia symptoms at this point in time, additional cross-sectional imaging was carried out without delay and if local tumour progression was confirmed or still suspected, patients were offered resection without delay. The remaining patients in the prolonged TTS group without suspicion of local tumour progression underwent additional evaluation with FDG—PET—CT 8-10 weeks after termination of nCRT, in order to exclude distant progression before proceeding to surgery 10-12 weeks after nCRT.

Surgical resection was carried out using transthoracic oesophagectomy with two-field lymphadenectomy, or optionally for Siewert type II tumours, total transhiatal extended gastrectomy. The surgical approach options included open, hybrid or total minimally invasive techniques.

Outcomes

The primary endpoint was histological complete response in the primary tumour (ypT0) in patients with AC. Histological complete response in the primary tumour in patients with SCC and in all patients together as well as tumour regression grade (TRG) were secondary endpoints. All surgical specimens were reviewed by an expert pathologist team at the Karolinska University Hospital in Stockholm, blinded to the allocated intervention. Due to the coronavirus disease 2019 pandemic, the specimens from the Cologne study site were re-assessed using digital slides instead of traditional glass slides. TRG was defined according to Chirieac[29] as the proportion of tumour cells to fibrosis in the primary tumour, assessed on a four-grade scale where TRG 1 represents histological complete response; TRG 2, 1%-10% remaining tumour cells; TRG 3, >10%-50% remaining tumour cells; and TRG 4, >50% remaining tumour cells. Other secondary endpoints included tumour resection rate, tumour-free resection margins using the Royal College of Pathologist's definition (no tumour cells within 1 mm of the resection margin), number of resected and metastatic lymph nodes, overall and progression-free survival in all patients and stratified by histologic type. Overall survival was defined as time from the end of nCRT until death from any cause. Progression-free survival was defined as time from the end of nCRT until first recurrence event, or death from any cause.

Statistical analysis

Data were mainly analysed according to the intention-to-treat (ITT) principle, although some per-protocol analyses were also carried out. The sample size was calculated based on results from the CROSS trial nCRT cohort.[9] To detect an increase in histological complete response from 23.6% to 43.1% in patients with AC, with a power of 80% and an α of

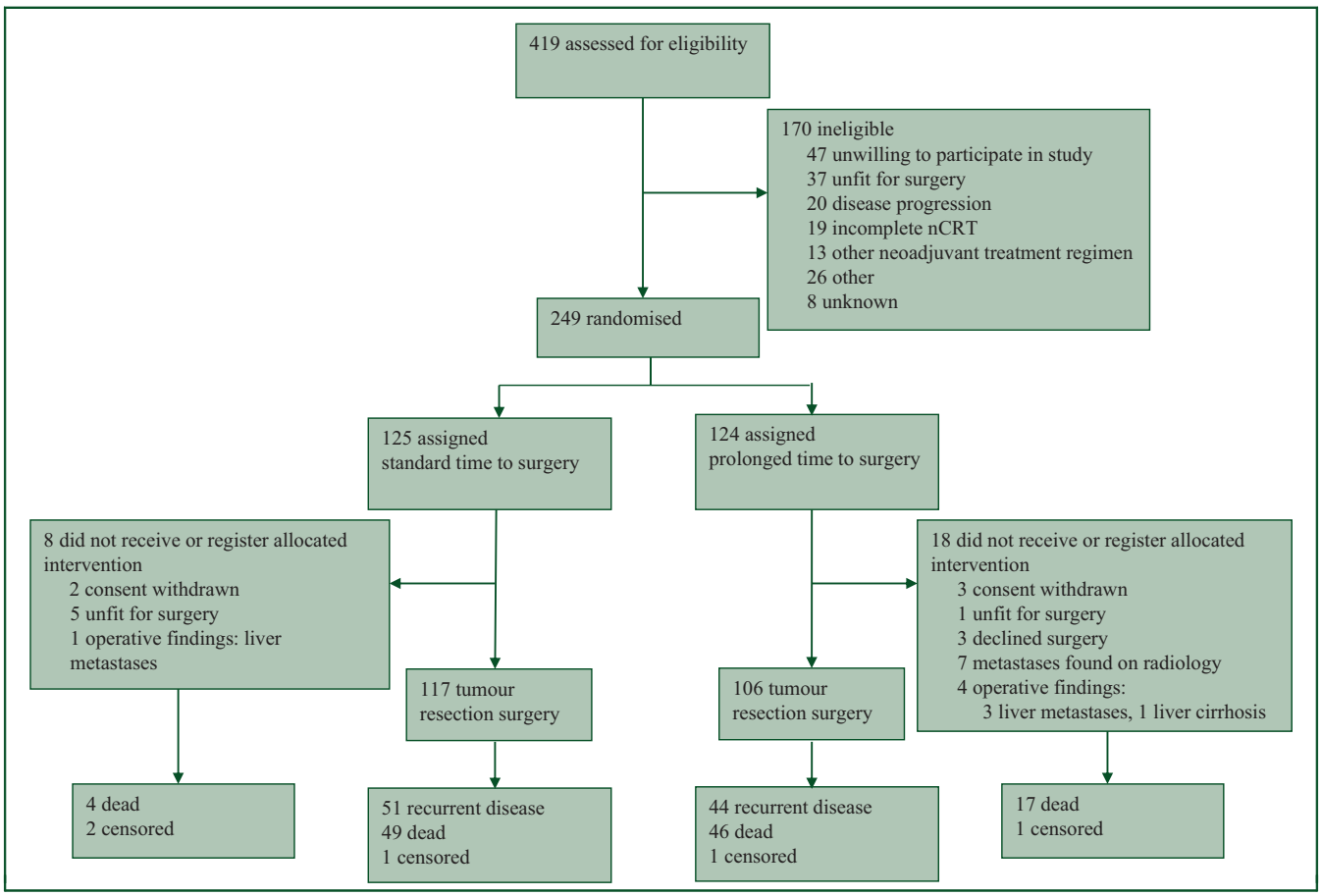

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the NeoRes II trial.

Table 1. Baseline characteristics

	Standard time to surgery 4-6 weeks	Prolonged time to surgery 10-12 weeks
Total, *n* (%)	125 (100)	124 (100)
Withdrawn consent, *n* (%)	2 (2)	3 (2)
Time to surgery, days/weeks		
Mean	40.2/5.7	75.8/10.8
Median	39.5/5.6	75/10.7
Range, days	26-102	42-109
Interquartile range, days	34-42	69-82
Age, mean years (range)	65 (34-78)	64 (42-79)
Sex, *n* (%)		
Female	22 (18)	18 (15)
Male	103 (83)	106 (86)
Smoking, *n* (%)		
Smoker	36 (29)	37 (30)
Previous smoker[a]	54 (43)	48 (39)
Nonsmoker	32 (26)	36 (29)
Missing data	3 (2)	3 (2)
Alcohol consumption, *n* (%)		
Overconsumption	5 (4)	6 (5)
Previous overconsumption[b]	4 (3)	2 (2)
No known overconsumption	116 (93)	116 (94)
Comorbidity, *n* (%)		
Diabetes mellitus	16 (13)	20 (16)
Cardiovascular disease	46 (37)	37 (30)
Chronic pulmonary disease	13 (10)	8 (7)
ECOG performance status, *n* (%)		
0	98 (78)	98 (79)
1	25 (20)	25 (20)
Missing data	2 (2)	1 (1)
Tumour location, *n* (%)		
Oesophagus or junctional type I	93 (74)	87 (70)
Junctional type II	32 (26)	36 (29)
Missing data	0 (0)	1 (1)
Histology, *n* (%)		
Adenocarcinoma	102 (82)	96 (77)
Squamous cell carcinoma	23 (18)	28 (23)
Clinical T-stage, *n* (%)		
T1	2 (2)	1 (1)
T2	31 (25)	29 (23)
T3	78 (62)	81 (65)
T4a	14 (11)	13 (11)
Clinical N-stage, *n* (%)		
N0	60 (48)	47 (38)
N1	48 (38)	57 (46)
N2	15 (12)	16 (13)
N3	2 (2)	4 (3)
Surgical approach, *n* (%)		
Minimally invasive	53 (42)	50 (40)
Hybrid minimally invasive	43 (34)	38 (31)
Open	21 (17)	18 (15)
No resection	6 (5)	15 (12)

ECOG, Eastern Cooperative Oncology Group.
[a]Stopped smoking >1 year ago.
[b]Overconsumption stopped >1 year ago.

0.05, we needed to evaluate 176 surgical specimens. To achieve this, we needed to randomise a surplus of patients to be evaluated on an ITT basis. The number of resected patients was monitored continuously, and enrolment stopped when the adequate number of patients had been resected. SCC patients were enrolled only for secondary endpoints. The sample size calculation was based on the primary endpoint complete histological response in the primary tumour in patients with AC.

Baseline characteristics of randomised patients were presented with frequency (percentage) for categorical variables or median (interquartile range) for continuous variables. For binomial outcomes, comparison was made using the chi-square test, or Fisher's exact test when the expected cell counts of a contingency table were below five. Patients' follow-up started at the date of randomisation and ended at the date of death, censoring for any reason, or planned end of follow-up. Overall survival was estimated using the Kaplan–Meier approach and log-rank tests were carried out for comparisons. Hazard ratios (HRs) and corresponding two-sided 95% confidence interval (95% CI) for overall survival were estimated using Cox regression models. Time since randomisation was used as the underlying timescale. Different histology and TRG levels were analysed separately. The proportional hazard assumption was tested with Schoenfeld residuals after fitting the Cox regression models. When evidence of non-proportional hazard was found, flexible parametric models were applied, allowing the effect of randomisation to vary over time.[30] A spline with 5 *df* was used for the baseline rate, and 2 *df* was used for the time-varying effect. Time-varying HRs for overall survival over time since randomisation were plotted separately for all patients and patients with AC, but not for patients with SCC due to no significant difference observed in the Kaplan–Meier survival curve.

Post hoc analyses were conducted to evaluate the overall survival across different patient subgroups. Because less than half (46.2%) of the patients died during follow-up, we calculated the difference in time at which mortality was 25% (i.e. 75% survival or first quartile survival) between treatment groups using the Kaplan–Meier approach. *P* values and 95% CI for comparisons for the difference in time when 25% of patients died between the groups were computed by the bootstrapping method with 1000 resamples. The bootstrap computes the variance by using deviations from the average of the replicates.

We repeated the analyses with progression-free survival as the outcome. Patients without disease progression or death were censored at the last available date of follow-up. Cox regression and Kaplan–Meier analysis were carried out to estimate the difference in progression-free survival. All tests were two-sided and a *P* value <0.05 was considered statistically significant. STATA® version 16 software (StataCorp LP, College Station, TX) was used for all statistical analyses.

RESULTS

Between 11 February 2015 and 28 March 2019, 419 patients were screened and 249 were enrolled in the trial and randomised. One hundred and twenty-five patients were assigned to standard TTS of 4-6 weeks, and 124 were assigned to prolonged TTS of 10-12 weeks. Two patients in the standard and three in the prolonged TTS group withdrew consent and were censored before treatment. In total, 223 patients (90%) underwent surgical resection, 117 (95%) in the standard TTS group and 106 (88%) in the prolonged TTS group ($P = 0.036$, Figure 1). In the standard TTS group, five patients (4%) were found unfit for surgery and one patient (1%) had an intraoperative finding of liver

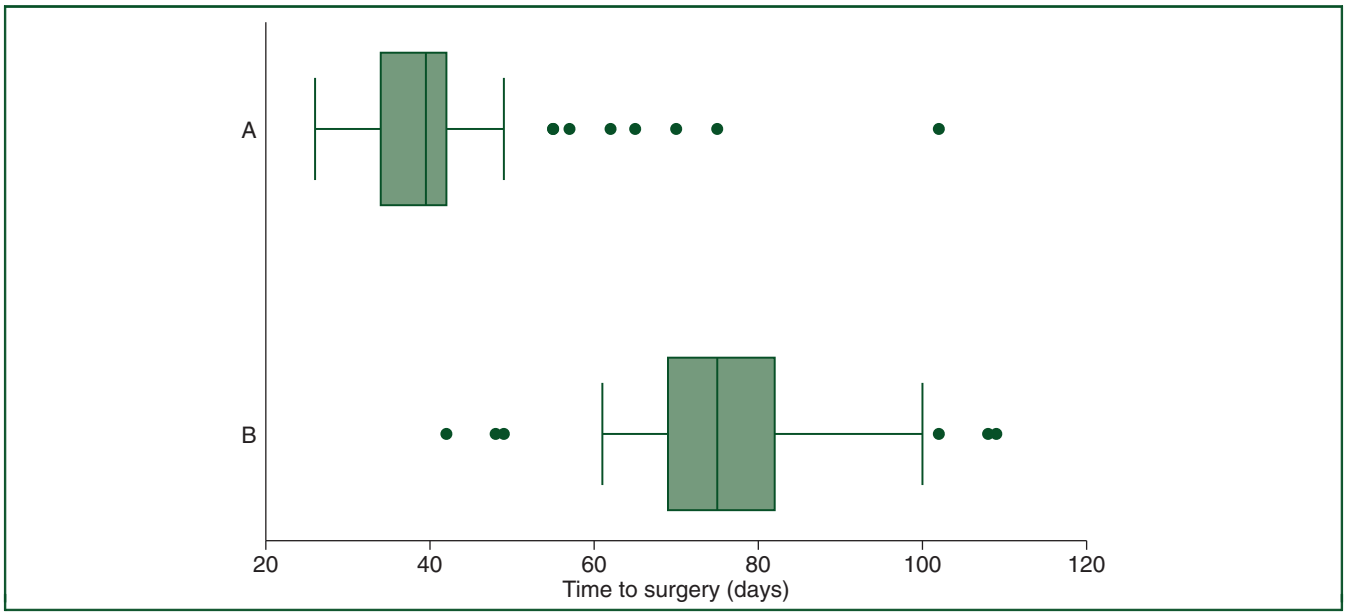

Figure 2. Distribution of patients' time to surgery in the two study arms. (A) Standard time to surgery. (B) Prolonged time to surgery.

metastases. In the prolonged TTS group, 3 patients (2%) declined surgery, 10 patients (8%) were not resected due to being diagnosed with distant metastatic disease at the additional FDG—PET—CT examination (7 patients) 8-10 weeks after terminated nCRT or at surgery (3 patients) and 1 patient (1%) was intraoperatively diagnosed with severe liver cirrhosis and therefore not resected (Figure 1).

Baseline characteristics were well balanced between the two intervention groups (Table 1). In the standard TTS group, the median TTS was 39.5 days (5 weeks and 4.5 days) and in the prolonged group it was 75 days (10 weeks and 5 days), showing that surgery was carried out well in accordance with the allocations per protocol (Figure 2). Three patients chose to cross over from standard to delayed TTS, while only one chose to cross over from delayed to the early TTS. Reasons for deviation from allocated time to surgery are described in Supplementary Table S2 (available at https://doi.org/10.1016/j.annonc.2023.08.010).

Allocation to prolonged TTS did not meet the statistical criteria for superiority versus standard delay of surgery regarding complete histological response in the primary tumour in patients with AC (26% versus 21%, $P = 0.429$, Table 2). There were no statistically significant differences between the allocated intervention groups regarding overall TRG, tumour-free resection margins, number of resected or metastatic lymph nodes, in either of the two histologic types, nor in all patients together (Table 2). Likewise, comparing those operated per protocol within the allocated timeframes in each group, there were no significant differences regarding TRG, tumour-free resection margins, number of resected or metastatic lymph nodes, detected in either of the two histologic types, nor in all patients together (Table 3).

The median follow-up time to death, censoring for any reason, or end of follow-up in all randomised patients was 36.4 months. At the last day of follow-up for these analyses, 72 (58%) patients allocated to standard and 62 (50%) patients allocated to prolonged TTS were alive. Of all patients enrolled, 25% allocated to standard TTS died by 26.5 (95% CI 16.9-34.0) months, whereas 25% of patients allocated to prolonged TTS died by 14.2 (95% CI 12.0-16.5) months, in effect a worse first quartile survival for this group (difference = 12.3, $P = 0.003$, 95% CI 3.7-21.0) (Figure 3). Considering all deceased patients, no overall difference in mortality was observed between patients allocated to prolonged compared to standard TTS over the whole study period (HR 1.35, 95% CI 0.94-1.95, $P = 0.107$). When considering time-varying HR, compared to patients allocated to standard TTS, patients allocated to prolonged TTS showed an elevated risk of mortality after 7 months (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.08.010). The risk declined rapidly after 10 months and decreased gradually thereafter: the HRs at 10, 20, 30 and 40 months were 3.09 (95% CI 1.44-6.61), 1.92 (95% CI 1.25-2.93), 1.08 (95% CI 0.67-1.74) and 0.49 (95% CI 0.22-1.11), respectively. For patients with AC, 25% mortality was reached after 29.7 (95% CI 16.7-36.0) months in patients allocated to standard and in 14.2 (95% CI 11.3-17.5) months in those allocated to prolonged TTS (Figure 3), demonstrating worse first quartile overall survival after prolonged TTS (difference = 15.5, $P = 0.002$, 95% CI 5.3-25.8). No overall significant difference in mortality was observed between these two groups in patients with AC over the whole study period (HR 1.43, 95% CI 0.95-2.2, $P = 0.089$). The greater risk of mortality was found between month 7 and month 23, whereafter the HR was not significantly associated with mortality (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.08.010). For patients with SCC allocated to standard TTS, 25% mortality occurred at 22 months (95% CI 1.7-29.1 months) and after prolonged TTS at 13.6 months (95% CI 7.1-23.9 months) (difference = 8.3, $P = 0.216$, 95% CI −7.8 to 24.0). Similar to all patients and those with AC, there was no

Table 2. Pathological outcomes by allocated time to surgery in all resected patients and stratified by histologic type

	Standard time to surgery, 4-6 weeks	Prolonged time to surgery, 10-12 weeks	*P* value
All resected patients, *n* (%)	117 (95)	106 (88)	0.036
Chirieac tumour regression grade, *n* (%)			0.181
1: No tumour cells[a]	31 (26)	32 (30)	0.541
2: 1%-10% tumour cells	40 (34)	23 (22)	
3: >10%-50% tumour cells	26 (22)	25 (24)	
4: >50% tumour cells	20 (17)	26 (25)	
Resection margins (<1 mm), *n* (%)			0.670
Free (R0)	115 (98)	103 (97)	
Involved (R1)	2 (2)	3 (3)	
Resected lymph nodes, median (IQR)	21 (14-31)	24 (15-31)	0.280
Lymph node metastasis, *n* (%)			0.687
ypN0	72 (62)	67 (64)	
ypN1-3	45 (38)	38 (36)	
Number of lymph node metastases, median (IQR)	0 (0-2)	0 (0-1)	0.781
Adenocarcinoma			
Surgical resection, *n* (%)	97 (95)	82 (87)	0.051
Chirieac tumour regression grade, *n* (%)			0.179
1: No tumour cells[a]	20 (21)	21 (26)	0.429
2: 1%-10% tumour cells	36 (37)	18 (22)	
3: >10%-50% tumour cells	23 (24)	23 (28)	
4: >50% tumour cells	18 (19)	20 (24)	
Resection margins (<1 mm), *n* (%)			0.662
Free (R0)	95 (98)	79 (96)	
Involved (R1)	2 (2)	3 (4)	
Resected lymph nodes, median (IQR)	20 (14-28)	25 (16-33)	0.053
Lymph node metastasis, *n* (%)			0.924
ypN0	61 (63)	51 (62)	
ypN1-3	36 (37)	31 (38)	
Number of lymph node metastases, median (IQR)	0 (0-2)	0 (0-1)	0.937
Squamous cell carcinoma			
Surgical resection, *n* (%)	20 (95)	24 (89)	0.621
Chirieac tumour regression grade, *n* (%)			0.649
1: No tumour cells[a]	11 (55)	11 (46)	0.545
2: 1%-10% tumour cells	4 (20)	5 (21)	
3: >10%-50% tumour cells	3 (15)	2 (8)	
4: >50% tumour cells	2 (10)	6 (25)	
Resection margins (<1 mm), *n* (%)			1.000
Free (R0)	20 (100)	24 (100)	
Involved (R1)	0 (0)	0 (0)	
Resected lymph nodes, median (IQR)	28.5 (13.5-42)	21 (14.5-25.5)	0.114
Lymph node metastasis, *n* (%)			0.429
ypN0	11 (55)	16 (67)	
ypN1-3	9 (45)	8 (33)	
Number of lymph node metastases, median (IQR)	0 (0-2)	0 (0-1)	0.389

IQR, interquartile range.
[a]Histological complete response in primary tumour (ypT).

difference in mortality over the whole study period in patients with SCC (HR 1.02, 95% CI 0.46-2.26, $P = 0.955$, Figure 3) between the allocated interventions. Overall survival stratified by TRG groups was similar between the allocated intervention groups, except in patients with TRG 4 (>50% remaining tumour cells), in which patients allocated to prolonged TTS had significantly worse survival (HR 2.5, 95% CI 1.1-5.8, Figure 4). Analyses of progression-free survival of the ITT population showed similar results as for overall survival (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.08.010). Per-protocol analyses of survival did not significantly differ between the intervention groups (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2023.08.010).

In a subgroup analysis for overall survival including age, sex, performance status, comorbidity, tumour location and clinical T- and N-stage, there were no subgroups with a significant overall survival difference between allocation to standard and prolonged TTS (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2023.08.010).

At the last day of follow-up for these analyses, in March 2022, 51 (44%) resected patients in the standard and 43 (41%) resected patients in the prolonged TTS group had a confirmed recurrence. There were no significant differences between patients allocated to standard compared to those allocated to prolonged TTS with regard to frequency of recurrence or site of recurrence (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.08.010).

DISCUSSION

In this study, the first randomised trial addressing the timing of surgery after nCRT for oesophageal cancer, prolonged TTS of 10-12 weeks after terminated nCRT was not associated

Table 3. Pathological outcomes in patients operated within allocated timeframes (per protocol)

	Standard time to surgery, 4-6 weeks	Prolonged time to surgery, 10-12 weeks	*P* value
All resected patients			
Operated within allocated timeframes, *n* (%)	88 (75)	67 (63)	0.052
Chirieac tumour regression grade, *n* (%)			0.176
1: No tumour cells[a]	23 (26)	18 (27)	0.919
2: 1%-10% tumour cells	34 (39)	16 (24)	
3: >10%-50% tumour cells	15 (17)	19 (28)	
4: >50% tumour cells	16 (18)	14 (21)	
Resection margins (<1 mm), *n* (%)			0.653
Free (R0)	86 (98)	64 (96)	
Involved (R1)	2 (2)	3 (4)	
Resected lymph nodes, median (IQR)	21 (14-30)	24 (17-31)	0.243
Lymph node metastasis, *n* (%)			0.508
ypN0	53 (60)	43 (65)	
ypN1-3	35 (40)	23 (34)	
Number of lymph node metastases, median (IQR)	0 (0-2)	0 (0-1)	0.737
Adenocarcinoma			
Operated within allocated timeframes, *n* (%)	72 (74)	55 (67)	0.294
Chirieac tumour regression grade, *n* (%)			0.136
1: No tumour cells[a]	13 (18)	11 (20)	0.782
2: 1%-10% tumour cells	31 (43)	14 (25)	
3: >10%-50% tumour cells	13 (18)	18 (33)	
4: >50% tumour cells	15 (21)	12 (22)	
Resection margins (<1 mm), *n* (%)			0.652
Free (R0)	70 (97)	52 (95)	
Involved (R1)	2 (3)	3 (5)	
Resected lymph nodes, median (IQR)	19.5 (14-27.5)	25 (17-32)	0.050
Lymph node metastasis, *n* (%)			0.731
ypN0	45 (63)	35 (65)	
ypN1-3	27 (38)	19 (35)	
Number of lymph node metastases, median (IQR)	0 (0-1.5)	0 (0-2)	0.948
Squamous cell carcinoma			
Operated within allocated timeframes, *n* (%)	16 (80)	12 (50)	0.039
Chirieac tumour regression grade, *n* (%)			0.928
1: No tumour cells[a]	10 (63)	7 (58)	1.000
2: 1%-10% tumour cells	3 (19)	2 (17)	
3: >10%-50% tumour cells	2 (13)	1 (8)	
4: >50% tumour cells	1 (6)	2 (17)	
Resection margins (<1 mm), *n* (%)			
Free (R0)	16 (100)	12 (100)	
Involved (R1)	0	0	
Resected lymph nodes per patient, median (IQR)	26.5 (13.5-42)	19.5 (13.5-26.5)	0.255
Lymph node metastasis, *n* (%)			0.459
ypN0	8 (50)	8 (67)	
ypN1-3	8 (50)	4 (33)	
Number of lymph node metastases, median (IQR)	0.5 (0-2)	0 (0-1)	0.353

IQR, interquartile range.
[a]Histological complete response in primary tumour (ypT0).

with better histological tumour response or any other improvement in pathological endpoints, compared to the standard TTS of 4-6 weeks. In addition, patients allocated to prolonged delay of surgery unexpectedly had worse first quartile overall survival, although not reaching statistical significance over the whole study period. In the subgroup of histological non-responders (TRG 4), patients allocated to prolonged TTS had significantly 2.5-fold worse overall survival, compared to those allocated to standard TTS. There was no significant difference in overall, locoregional, distant or combined locoregional—distant recurrences in surgically resected patients allocated to prolonged compared to standard TTS, nor between those operated per protocol within the standard and prolonged timeframes.

Several previous observational studies have suggested that an increase in the TTS increases tumour regression,[9,17-19,23,26] while others have not been able to show any such association.[12,13,24] In this randomised trial there was no association, in the ITT and per-protocol populations alike, between prolonged TTS after nCRT and complete histological response, nor with tumour regression overall. In addition, there were no associations whatsoever between prolonged TTS and the rate of tumour-free resection margins, nor with the number of metastatic lymph nodes. This provides high-validity evidence against any advantage in pathological endpoints after prolonged compared to standard TTS after nCRT, contradicting the main hypothesis of the study.

The published body of data addressing prolonged versus standard TTS after nCRT from observational studies is likely to be affected by selection bias in several ways. Firstly, delay of surgery beyond the standard clinical practice TTS may be

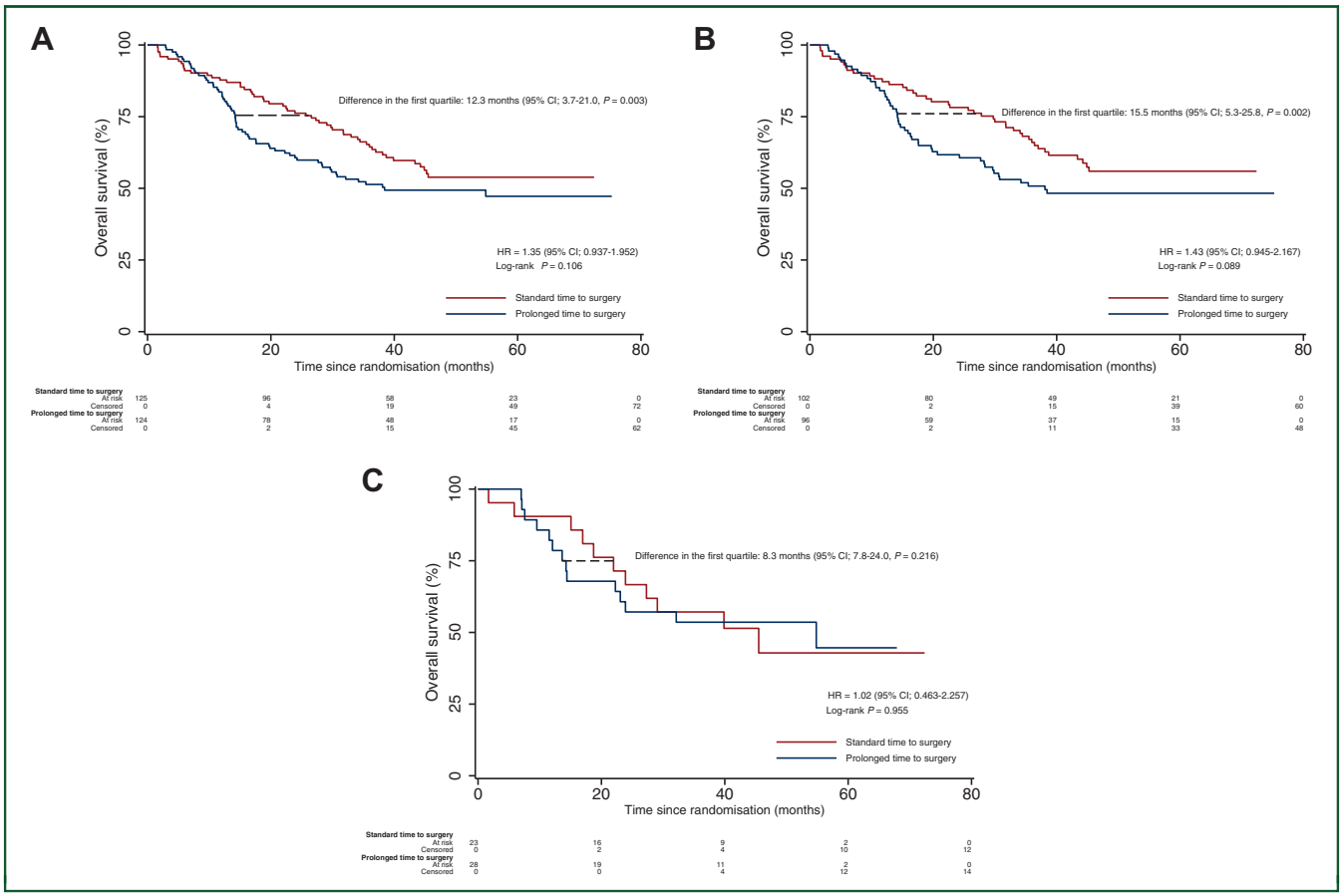

Figure 3. Overall survival including all randomised patients (A), patients with adenocarcinoma (B) and patients with squamous cell carcinoma (C).
CI, confidence interval; HR, hazard ratio.

because of side-effects of nCRT, with poor performance status and a need to recover for an additional number of weeks, which could act to select physiologically more vulnerable patients to delayed surgery. In addition, acting in the other direction, patients undergoing resection after delayed restaging are likely to be a selection of patients in whom late interval metastases have been excluded, making them more prone to long-term survival.

Most published observational studies, all likely to be affected by the selection bias effects described above, have not reported any difference in survival comparing those operated after standard delay of less than 6 or 7 weeks to those with longer delay of surgery after nCRT. In contrast, this first randomised study to compare survival after standard versus prolonged TTS showed an unexpected difference, with significantly shorter first quartile (75% alive) overall survival, although not reaching statistical significance for the whole time period, after prolonged delay of surgery. Patients with TRG 4, in effect pathological non-responders, fared particularly badly after prolonged TTS, with a statistically significant 2.5-fold worse overall survival compared to patients allocated to standard TTS. The relatively large difference in overall survival in this subgroup is likely to be one of the drivers behind the poorer survival observed after prolonged TTS in the whole study. The survival disadvantage of prolonged TTS in pathological non-responders is particularly alarming as extensive measures, including an additional endoscopy and dysphagia assessment and in case of remaining suspicion additional cross-sectional imaging, were taken to find clinical non-responders at 4-6 weeks after nCRT. Those patients in whom any suspicion remained of non-response or even progression at this point were offered crossover to surgery without further delay.

The finding that there was no difference in the incidence or site of recurrences, and particularly no advantage for prolonged TTS with regard to locoregional recurrence, provides further evidence against our hypothesis that prolonging TTS, by increasing tumour regression and the tumour-free resection margins, would lead to better locoregional tumour control.

Among patients allocated to prolonged TTS, 10 (8%) were diagnosed with distant metastases, precluding resective surgery, compared to only 1 (1%) in the standard TTS arm. This should be acknowledged as a likely advantage of prolonged TTS for this subgroup of patients.

The strengths of the study include the randomised allocation of the TTS after nCRT, the meticulous follow-up and data monitoring and the careful and blinded assessment of all pathological specimens by one dedicated team of pathologists. Another strength of the trial is that treatment allocation worked well in accordance with the protocol in

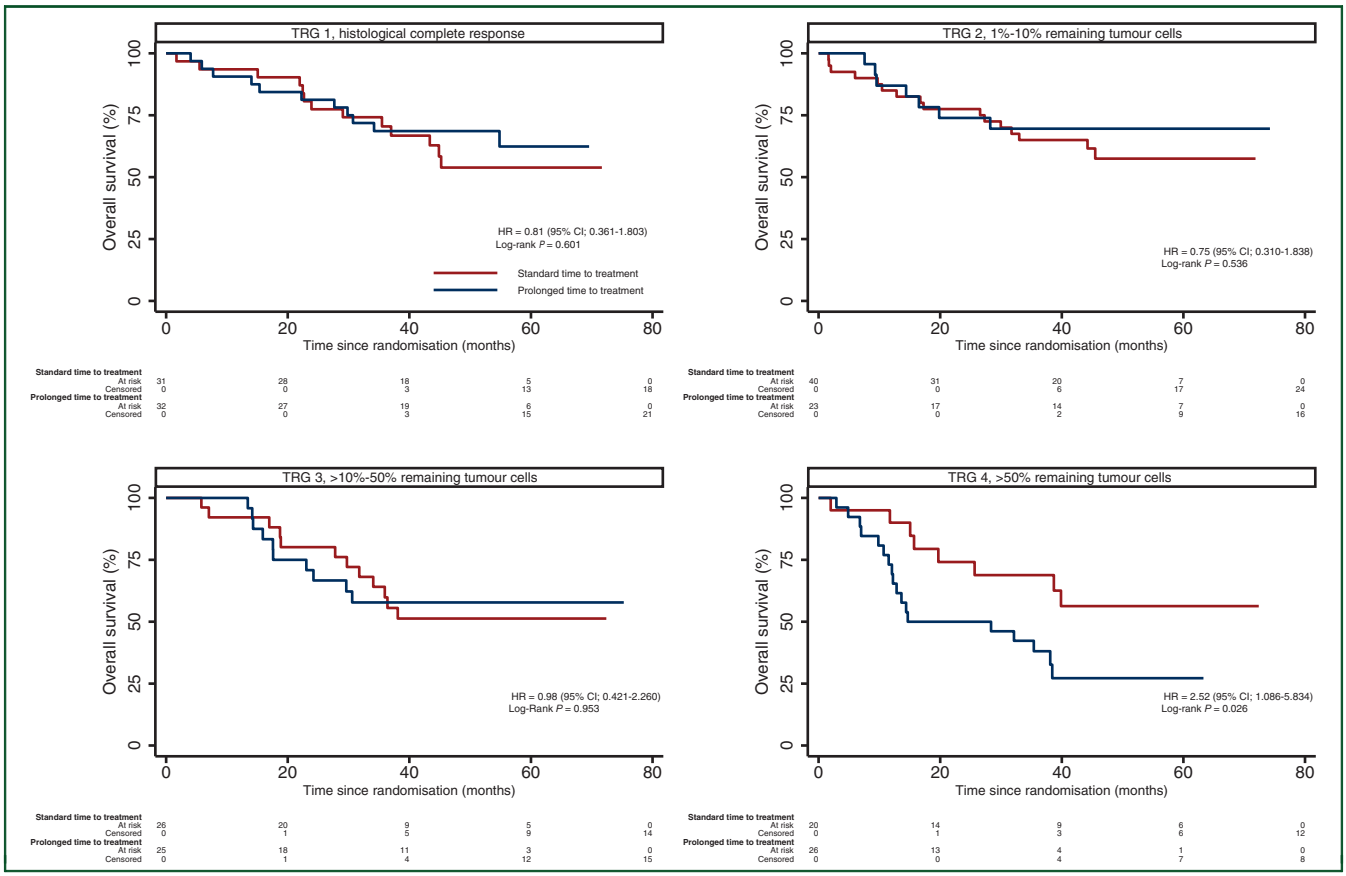

Figure 4. Overall survival including all resected patients by tumour regression grade according to Chirieac.
CI, confidence interval; HR, hazard ratio.

the sense that the median TTS in the standard and prolonged TTS groups were well within the pre-defined timeframes.

A potential weakness of the study is that all patients were not operated per protocol within the allocated predefined timeframes. In the standard TTS group, surgery was delayed >7 weeks in eight patients, mainly because they were severely affected by the treatment and not considered operable within 6 weeks of completed nCRT. However, these eight patients are a small proportion of those operated after allocation to standard delay (7%) and in addition postponing surgery until patients have recovered is in accordance with how these patients would have been managed in clinical practice, which strengthens the external validity of the trial. Another potential weakness of the trial is that patients aged >80 years or with severe comorbidity were not included.

In conclusion, prolonged TTS did not improve histological complete response or other pathological endpoints, while there was a strong trend towards worse overall survival, suggesting caution in routinely delaying surgery for >6 weeks after nCRT.

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DISCLOSURE

The author have declared no conflicts of interest.

DATA SHARING

Requests of sharing deidentified participant data from this paper will be considered on a case-by-case basis. A detailed proposal for how the data will be used is required and a data access agreement must be signed. Please send enquiries to the corresponding author.

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