Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastro-esophageal junction. Long-term results of a randomized clinical trial.

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Abstract

NeoRes I is a randomized phase II trial comparing neoadjuvant chemoradiotherapy with neoadjuvant chemotherapy in the treatment of resectable cancer of the esophagus or gastro-esophageal junction. Patients with biopsy-proven adenocarcinoma or squamous cell carcinoma, T1N1 or T2-3N0-1 and M0-M1a (AJCC 6th edition) were randomized to receive three 3-weekly cycles of cisplatin 100 mg/m^2 day 1 and fluorouracil 750 mg/m^2/24 hours, days 1-5 with or without the addition of concurrent radiotherapy 40 Gy, 2 Gy/fraction, 5 days a week, followed by esophageal resection with two-field lymphadenectomy. Primary endpoint was complete histopathological response rate in the primary tumor. Survival and recurrence patterns were evaluated as secondary endpoints. Between 2006 and 2013, 181 patients were enrolled in nine participating institutions in Sweden and Norway. All three chemotherapy cycles were delivered to 73% of those allocated to chemoradiotherapy, and to 86% of those allocated to chemotherapy. 87% of those allocated to chemoradiotherapy received full dose radiotherapy. 86% in the chemotherapy group and 87% in the chemoradiotherapy group underwent tumor resection. Initial results showed that patients allocated to chemoradiotherapy more often responded with complete histopathological response in the primary tumor (28% versus 9%). Treatment-related complications were similar between the groups although postoperative complications were more severe in the chemoradiotherapy group. In this article we report the long-term results. Five-year progression-free survival was 38.9% (95% CI 28.9%-48.8%) in the chemoradiotherapy group versus 33.0% (95% CI 23.6%-42.7%) in the chemotherapy group, p=0.82. Five-year overall survival was 42.2% (95% CI 31.9%-52.1%) versus 39.6% (95% CI 29.5%-49.4%), p=0.60. There were no differences in recurrence patterns between the treatment groups. This is to our knowledge the largest completed randomized trial comparing neoadjuvant chemotherapy with neoadjuvant chemoradiotherapy followed be esophageal resection in patients with cancer in the esophagus or gastro-esophageal junction. Despite a higher tumor tissue response in those who received neoadjuvant chemoradiotherapy, no survival advantages were seen. Consequently, the results do not support unselected addition of radiotherapy to neoadjuvant chemotherapy as standard of care in patients with resectable esophageal cancer.

Introduction

Esophageal cancer is the twelfth most common cancer worldwide. The prognosis is gloomy visualized by the fact that it is the seventh leading cause of cancer related death[1]. Neoadjuvant treatment in addition to surgery has in meta-analysis been shown to improve survival compared to surgery alone in resectable esophageal cancer. Indirect comparison has shown a trend towards survival benefit from neoadjuvant chemoradiotherapy when compared to neoadjuvant chemotherapy[2]. Direct comparisons provide a higher level of evidence, and prior to this trial there have been two randomized clinical trials comparing the effect of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy followed by surgery in esophageal adenocarcinoma[3-5]. In both trials chemoradiotherapy provided a higher rate of complete histopathological response without a statistically significant gain in survival. As far as we know, no corresponding comparative trials have been completed in patients with squamous cell carcinoma.

The present trial, NeoRes (**Neo**adjuvant therapy for **Res**ectable Esophageal cancer), compared neoadjuvant chemoradiotherapy with neoadjuvant chemotherapy in patients with resectable adenocarcinoma or squamous cell carcinoma in the esophagus or gastro-esophageal junction. Between 2006 and 2013, 181 patients were enrolled in Sweden and Norway. Accrual was initially slow and more sites joined the trial during the study period. Surgery was performed at seven different sites. First results were published in 2016[6]. The primary endpoint was met with a gain in complete histopathological response in the resected primary tumor (28% versus 9%) for those treated with chemoradiotherapy. We also found that the radical resection rate was higher (87% versus 74%) and the presence of metastatic lymph nodes at resection was lower (39% versus 64%) in the chemoradiotherapy group. There was no difference in 3-year survival between the groups (49% versus 47%).

In this article we analyze overall survival, progression-free survival and recurrence patterns.

Materials and methods

Study design

This prospective randomized phase II trial was approved by Research Ethics Committees in Sweden and Norway. All participating patients provided written informed consent. Patients were stratified by histological tumor type and randomised independently by a computerized software at the Regional Oncological Centre in Stockholm. The allocation sequence was concealed to all investigators. The registration number in the Clinical Trials Database is NCT01362127. No commercial support was given to this study.

Eligibility criteria

Patients with histologically proven adenocarcinoma or squamous cell carcinoma of the esophagus or esophagogastric junction (Siewert type I and II)[7] with the clinical stages T1N1 or T2-3N0-1 and M0-M1a according to the American Joint Committee on Cancer tumor-nodes-metastasis staging system 6th edition were eligible for inclusion. Patients with cancer in the proximal third were eligible provided that radical resection could be completed without laryngectomy. Eligible patients were ≤ 75 years, had an Eastern Cooperative Oncology Group performance status of 0 to 1, were free from uncontrolled

cardiac disease including a myocardial infarction within 12 months, and had no complications from diabetes. All had hematological and renal function within normal limits. A computed tomography of the thorax and abdomen within one month from randomization was required. Pre-treatment positron emission tomography (PET) and endoscopic ultrasound were optional.

Treatment

Chemotherapy

All patients were scheduled for three 3-weekly cycles of cisplatin 100 mg/m^2 day 1 and fluorouracil 750 mg/m^2/24 hours, days 1-5. In case of hearing impairment, tinnitus or renal dysfunction cisplatin was replaced by carboplatin (AUC 5) in patients with squamous cell carcinoma or oxaliplatin 130 mg/m^2 in patients with adenocarcinoma.

Radiotherapy

Patients randomized to receive chemoradiotherapy were planned to receive 40 Gy concomitant with chemotherapy cycle 2 and 3 (2 Gy once daily in 20 fractions, 5 days a week) with a photon beam linear accelerator. A three-dimensional dose planning system was used. For tumors located mainly above the carina, the caudal border of the clinical target volume (CTV) was 5 cm below the tumor and the supraclavicular nodes defined the upper border. For tumors located mainly below the carina, the cranial border of the CTV was 5 cm cranial of the tumor and the lower border was defined by the celiac lymph nodes. In the lateral, anterior, and posterior directions, the CTV should embrace the gross tumor volume and paraesophageal area with a margin of 1 cm, but also respecting anatomical barriers such as pleura, pericardium, and bone. The planning target volume was according to local routines. The dose to the lungs exceeding 20 Gy was kept as low as possible and was not to exceed one third of the lung volume. The volume of the heart that received ≥30 Gy was kept to a minimum. The dose to both kidneys was not to exceed 12 Gy, and the dose to one kidney was not to exceed 20 Gy. Maximum dose to the spinal cord was 40 Gy.

Surgery

Surgery was performed 4-6 weeks after completion of the neoadjuvant treatment. The recommended operation for cancers in the cardia and in the distal third of the esophagus was a thoracoabdominal Ivor-Lewis resection with an intrathoracic anastomosis, whereas a three-stage-resection was recommended for cancers in the middle and upper part of the esophagus. Two field lymphadenectomy was strived for.

Follow up

Follow up visits were planned every 3 months during the first 2 years, and then every 6 months until 5 years after the end of treatment. CT and/or endoscopy was made on clinical suspicion of recurrent disease.

Statistical analysis

The trial required randomization of 172 eligible patients to have a statistical power to detect an improvement of 15 % in complete histological response in the primary tumor with the use of a two-sided test with 0,80 statistical power and a significance level of 0,05. Progression-free survival, overall survival and recurrence patterns were evaluated

as secondary endpoints. At randomization patients were stratified on histology. The time-to-event was estimated with the Kaplan Meier method with the log-rank test to ascertain significance. Progression-free survival was defined as the time from registration until progression or death from any cause. For patients who did not undergo tumor resection, time for progression was set at the date when decision was made not to proceed to surgery. Overall survival was defined as the time from registration until death. Living patients were censored at 60 months after randomization. Data were analyzed according to an intention-to-treat principle. We used cox proportional hazard models for univariate and multivariate analysis of factors with potential prognostic relevance for survival. Binominal logistic regression was used to ascertain effects of baseline characteristics on patterns of recurrence and histopathological response. Associations between categorical variables were tested with Fisher´s exact test and Chi-square test for association. The differences were considered significant at the 5% level ($p < 0.05$). Data were analyzed with Stata software, version 14.0.

Results

Baseline characteristics were well balanced between the treatment groups (Table 1). The flow chart of the trial is presented in Figure 1.

Treatment delivery

Three cycles of chemotherapy were delivered to 74% in the chemoradiotherapy group and to 86% in the chemotherapy group. Among those allocated to chemoradiotherapy 87% received full dose radiotherapy. Among those allocated to chemoradiotherapy 87% received full dose radiotherapy. Tumor resection rate was 87% (chemoradiotherapy group) and 86% (chemotherapy group). Details are presented in Table 2.

Survival

All patients were followed until death or until 60 months after randomization.

Median overall survival was 31.4 months (95% CI 20.9-60.0) in patients in the chemoradiotherapy group and 36.0 months (95% CI 22.4-59.6) in patients in the chemotherapy group. Overall survival at five years reached 42.2% (95% CI 31.9%-52.1%) in the chemoradiotherapy group and 39.6% (95% CI 29.5%-49.4%) in the chemotherapy group, p= 0.60.

Median overall survival was 30.8 months (95% CI 20.6-52.3) in patients with adenocarcinoma and 60.0 months (95% CI 23.7-60.0) in patients with squamous cell carcinoma, p=0.48.

Progression-free survival at five years reached 38.9% (95% CI 28.9%-48.8%) in the chemoradiotherapy group and 33.0% (95% CI 23.6%-42.7%) in the chemotherapy group, p= 0.82.

Median progression-free survival was 19.5 months (95% CI 13.6-33.7) in patients with adenocarcinoma and 49.4% months (95% CI 20.9-60.0) in patients with squamous cell carcinoma, p=0.17.

In patients with complete histological response in the primary tumor as defined in the initial report[6], 5-year survival rate was 75.9% (95% CI 55.9%-87.7%) compared to 40.5% (95% CI 31.9%-48.9%) in those who did not achieve complete histological response, p< 0.001. A logistic regression was performed to ascertain the effects of age, performance status, sex, histology, treatment, clinical T- and N-stage on the likelihood to achieve complete histopathological response. Patients with squamous cell carcinoma were 2.49 times more likely to respond with complete histopathological response than those with adenocarcinoma (p=0.049). As previously reported, treatment with chemoradiotherapy was associated with a higher rate of complete histopathological response than chemotherapy.

Among patients allocated to chemotherapy, 72 underwent tumor resection after at least two cycles of chemotherapy and no radiotherapy. Among patients allocated to chemoradiotherapy, 69 underwent tumor resection after at least two cycles of chemotherapy and at least 30 Gy. These patients are included in the per protocol analysis which showed that 5-year overall survival was 47.8% (95% CI 35.7%-59.0%) after chemoradiotherapy and surgery compared to 44.4% (95% CI 32.8%-55.5%) after chemotherapy and surgery, p= 0.27.

Survival curves are displayed in Figure 2.

Impact of risk factors on overall survival

Pre-treatment characteristics that might affect survival are displayed in Table 3. Female sex, lower clinical T-stage and squamous cell carcinoma tended to have a more favourable prognosis compared to male sex, lower clinical T-stage and adenocarcinoma.

To assess if certain patient groups had an increased likelihood of improved survival with chemotherapy or chemoradiotherapy, a Cox regression analysis with adjustment for baseline variables were used. As shown in Figure 3 none of the two treatment options seem to offer any advantage to a specific group of patients as specified by their different baseline characteristics.

Recurrence patterns

All recurrences were diagnosed with a computed tomography, histology or both.

Among patients who underwent tumor resection, 34 patients (44%) in the chemoradiotherapy group and 41 patients (53%) in the chemotherapy group experienced a recurrence (p=0.27).

Potential prognostic factors predicting patterns of recurrence were analyzed as detailed in Table 4. Peripheral metastases were more common as the first site of recurrence in patients with adenocarcinoma than in patients with squamous cell carcinoma. There were no differences in frequency or patterns of recurrence between the treatment groups.

Causes of death

At the time of the analysis 52(58%) patients in the chemoradiotherapy group and 55(60%) patients in the chemotherapy group had died. There were significantly more patients who died from postoperative complications among those allocated to chemoradiotherapy. Otherwise there were no differences between the treatment groups as specified in Table 5.

Discussion

These long-term results confirm our initial report that there is no difference in survival between those who received neoadjuvant chemoradiotherapy compared to those who received neoadjuvant chemotherapy prior to esophageal resection for adenocarcinoma or squamous cell carcinoma in the esophagus or gastro-esophageal junction.

The present trial is to our knowledge the largest completed randomized trial evaluating the addition of radiotherapy to neoadjuvant chemotherapy in esophageal carcinoma, and also the one including most patients with adenocarcinoma. In this trial, as well as in the other two published randomized trials addressing the same question[3-5], the tumor response rate was higher among those receiving radiotherapy. This was however not translated into better survival in any of the trials, although there was an almost significant trend towards better survival among those receiving chemoradiotherapy in the German trial. There were slight differences in radiotherapy doses, yet the German trial with the seemingly best survival benefit from the addition of radiotherapy used the lowest doses. On the other hand, in that trial less extensive lymph node dissection was practiced with only 48% of the patients who underwent tumor resection being operated on with a thoraco-abdominal approach. This is to be compared with 83% in the present trial and 100% in the Australian trial. Therefore, a possible explanation for the lack of survival benefit despite better tumor response could be that the addition of radiotherapy may not increase local tumor control when extensive lymph node dissection is used. This hypothesis is supported by the fact that there were fewer loco-regional recurrences among those who received radiotherapy in the German trial as opposed to the present trial and the Australian trial when more extensive surgery was practiced. Another possible explanation to the lack of survival benefit despite better tumor response could be that more patients treated with chemoradiotherapy died from post-operative complications. In a recent meta-analysis neoadjuvant chemoradiotherapy tended to increase postoperative mortality which was not seen after neoadjuvant chemotherapy, even though direct comparison could not prove any difference between the two treatment options[8]. Furthermore, one has to bear in mind that the present trial was designed to distinguish a difference in complete histological response and is accordingly underpowered for the survival analyses.

Still, complete response is a well-established predictor of survival after neoadjuvant treatment[9] and this is also confirmed in the present study. It has previously been shown that there is a correlation between radiosensitivity and chemosensitivity in tumor-tissue[10-12]. Consequently, a good pathological response in the primary tumor from chemotherapy is likely to become even better by the addition of radiotherapy but with no survival benefit if followed by extensive surgery. However, complete histopathological response at the primary site also indicates response on peripheral micrometastases from chemotherapy which could partly explain why it is a prognostic marker for survival.

We found female sex to be an independent favorable prognostic factor. This has previously been described even though the reason remains unclear[13]. Further exploitation of this matter might give more insight into the pathogenesis of the disease.

After treatment with surgery alone for resectable esophageal cancer, patients with adenocarcinoma have a better survival than patients with squamous cell carcinoma[14]. However, our results show that after the addition of neoadjuvant treatment, patients with squamous cell carcinoma have at least as favorable prognosis, and even tend to have better prognosis than those with adenocarcinoma. The survival curves from the CROSS-trial[15,16] display the same tendency, also suggesting that squamous cell carcinoma is more sensitive to and carry the potential to benefit even more from current neoadjuvant treatment strategies than adenocarcinoma. The differences in tumor biology between squamous cell carcinoma and adenocarcinoma are further highlighted by the differences in recurrence patterns as peripheral metastases were more common as first site of recurrence in patients with adenocarcinoma. In recently published data the same pattern is seen after definitive chemoradiotherapy[17]. Moreover, we found a higher proportion of complete histopathological response in squamous cell carcinoma again confirming data from the CROSS-trial[15,16]. All together this implies that the two different histology types could well benefit from different treatment strategies. Our data, as well as data from Burmeister et al, suggest that patients with adenocarcinoma might not benefit from the addition of radiotherapy to neoadjuvant chemotherapy. Both these trials used cisplatin and fluorouracil which remain to be the most well documented chemotherapeutic drugs in the treatment of esophageal cancer[18]. Nonetheless, new drugs have entered the arena and the potential advantage from the addition of radiotherapy to neoadjuvant chemotherapy-regimens including taxanes is currently under investigation in the ongoing trials ESOPEC and Neo-AEGIS. On the other hand, as squamous cell carcinoma seems to be more sensitive to oncological treatment than adenocarcinoma, it might be that some patients in the future can be spared surgery provided that tumor response can be assessed in a reliable way.

In conclusion, this mature analysis of the to date largest completed randomized trial comparing neoadjuvant chemoradiotherapy to neoadjuvant chemotherapy in esophageal and junctional cancer provides no evidence of survival advantage from the addition of radiotherapy, despite better tumor response. Consequently, the results do not support unselected addition of radiotherapy to neoadjuvant chemotherapy as standard of care.

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Table 1
Demographic and disease-specific characteristics of patients enrolled in the study

	Patients assigned to receive chemoradiotherapy (n=90)	**Patients assigned to receive chemotherapy (n=91)**
Median age (range)	63 (37-75)	63 (38-75)
Sex		
Male	72	77
Female	18	14
ECOG Performance status		
0	75	77
1	15	14
Histology		
Adenocarcinoma	65	66
Squamous cell carcinoma	25	25
Tumour location		
Proximal	2	2
Mid	13	13
Distal	60[‡]	59
Gastro-esophageal junction	15[‡]	17
Clinical T-stage[†]		
1	1	1
2	31	31
3	58	59
Clinical N-stage[†]		
0	33	34
1	57	57

Data are number of patients unless otherwise indicated

[†]American Joint Committee on Cancer tumor-nodes-metastasis staging system 6th edition
Abbreviation: ECOG; Eastern Cooperative Oncology Group

[‡]In the first publication one patient having a cancer in the gastro-esophageal junction was described to have a distal cancer. Previous typing errors had no effect on earlier published results.

Table 2
Treatment delivery

Delivered treatment	Patients assigned to receive chemoradiotherapy (n=90)	Patients assigned to receive chemotherapy (n=91)	p-value
Chemotherapy, 3 cycles	67 (74%)	78 (86%)	0.06[§]
Full dose radiotherapy	78(87%)[†]	1(1%)[†]	
Surgical resection	78(87%)	78(86%)	0.85[§]
Ivor Lewis esophagectomy	49(63%)[‡]	54(69%)[‡]	0.51[§]
Three-stage esophagectomy	19(24%)[‡]	16(21%)[‡]	0.55[§]
Transhiatal esophagectomy	8(10%)[‡]	7(9%)[‡]	0.77[§]
Total gastrectomy	2(3%)[‡]	1(1%)[‡]	0.62[¶]
No resection	12(13%)	13(14%)	0.85[§]

Data are number of patients unless otherwise indicated

[†]Number is updated since the first publication. Three patients among those assigned to receive chemoradiotherapy were incorrectly reported not to have received full dose. One patient among those assigned to receive chemotherapy was given 40 Gy.

[‡]Percent of those resected

[§] Chi-square test for association

[¶] Fisher exact test

Table 3 The association between pre-treatment characteristics and overall survival

	Number of patients	**Univariate analysis**		**Multivariate analysis**	
		Crude hazard ratio (95% CI)[†]	*p-value*	*Adjusted hazard ratio (95% CI)*[‡]	*p-value*
Age					
≤60	66	1.00		1.00	
>60	115	1.06 (0.71-1.58)	0.78	1.03 (0.68-1.54)	0.90
Sex					
Male	149	1.00		1.00	
Female	32	0.56 (0.32-0.98)	0.04	0.57 (0.33-1.01)	0.05
ECOG Performance Status					
0	152	1.00		1.00	
1	29	0.71 (0.41-1.25)	0.24	0.66 (0.37-1.17)	0.16
Tumour location					
Cardia/distal	151	1.00		1.00	
Proximal/middle	30	1.05 (0.64-1.73)	0.84	1.39 (0.78-2.45)	0.26
Histology					
Squamous cell carcinoma	50	1.00		1.00	
Adenocarcinoma	131	1.40 (0.89-2.21)	0.15	1.69 (0.98-2.89)	0.06
Clinical T-stage					
1-2	64	1.00		1.00	
3	117	1.47 (0.97-2.23)	0.07	1.60 (1.01-2.54)	0.05
Clinical N-stage					
0	67	1.00		1.00	
1	114	1.20 (0.81-1.78)	0.37	1.16 (0.74-1.82)	0.52

Abbreviation: CI; confidence interval. ECOG; Eastern Cooperative Oncology Group

[†] Crude hazard ratios and 95% confidence intervals were obtained using univariate Cox proportional hazard regression models.

[‡] Adjusted hazard ratios and 95% confidence intervals were obtained using multivariate Cox proportional hazard regression models, adjusting for age, sex, performance status, tumour location, histology, clinical T- and N-stage.

Table 4 Potential prognostic factors for primary site of recurrence for patients who underwent tumor resection

	Total number of patients (n=156)	**Locoregional recurrence with or without distant recurrence** (n=38)		**Distant recurrence with or without locoregional recurrence** (n=60)	
		Number of patients (%)	*Odds ratio (95% CI)*	*Number of patients (%)*	*Odds ratio (95% CI)*
Age					
≤60	59	18(30.5%)	1.00	22(37.2%)	1.00
>60	97	20(20.6%)	0.55 (0.26-1.19)	38(39.2%)	1.07 (0.52-2.19)
Sex					
Male	126	32(25.4%)	1.00	52(41.2%)	1.00
Female	30	6(20.0%)	0.75 (0.29-2.14)	8(26.7%)	0.50 (0.20-1.28)
ECOG Performance status					
0	132	35(26.5%)	1.00	53(40.2%)	1.00
1	24	3(12.5%)	0.37 (0.10-1.36)	7(29.2%)	0.50 (0.18-1.41)
Histology					
Squamous cell carcinoma	43	8(18.6%)	1.00	11(25.6%)	1.00
Adeno-carcinoma	113	30(28.3%)	1.42 (0.57-3.51)	49(43.3%)	2.72 (1.17-6.31)*
Clinical T-stage					
1-2	56	15(26.8%)	1.00	16(28.6%)	1.00
3	100	23(23.0%)	1.09 (0.47-2.53)	44(44.0%)	2.08 (0.93-4.63)
Clinical N-stage					
0	61	17(27.9%)	1.00	19(31.1%)	1.00
1	95	21(22.1%)	0.79 (0.35-1.80)	41(43.2%)	1.77 (0.82-3.85)
Allocated treatment					
Chemo-radiotherapy	78	18(23.1%)	1.00	26(33.3%)	1.00
Chemo-therapy	78	20(25.6%)	1.05 (0.50-2.22)	34(43.6%)	1.59 (0.80-3.17)

Abbreviation: CI; confidence interval. Odds ratio and 95% confidence intervals were obtained using multivariate unconditional logistic regression models, adjusting for age, sex, performance status, histology, clinical T and N-stage and allocated treatment.
* $p < 0.05$.

Table 5 Cause of death

Cause of death	Patients assigned to receive chemoradiotherapy (n=90)	Patients assigned to receive chemotherapy (n=91)	p-value
Esophageal cancer	41(46%)	47(52%)	0.41†
Other disease	2(2%)	6(7%)	0.28‡
Post-operative complication	8(9%)	1(1%)	0.02‡
Anastomotic leakage	3	1	
Respiratory complication	2		
Aorto-esophageal fistula	1		
Gastric conduit necrosis	1		
Multi organ failure	1		
Side-effect from neoadjuvant treatment	1(1%)	1(1%)	1.00‡
Total	52(58%)	55(60%)	0.72†

Data are number of patients unless otherwise indicated

† Chi-square test for association

‡ Fisher exact test

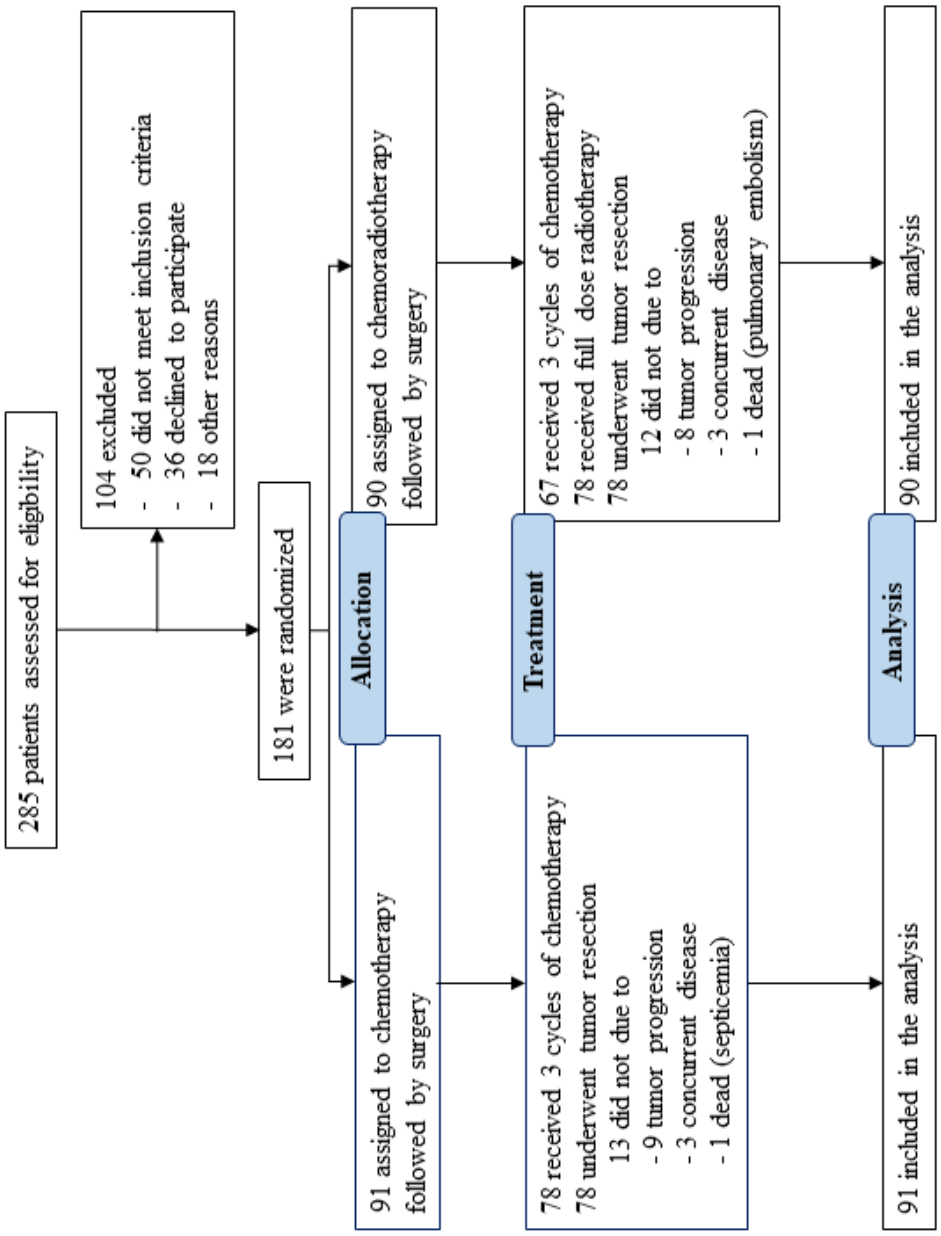

Figure 1 Flow chart of the NeoRes I trial

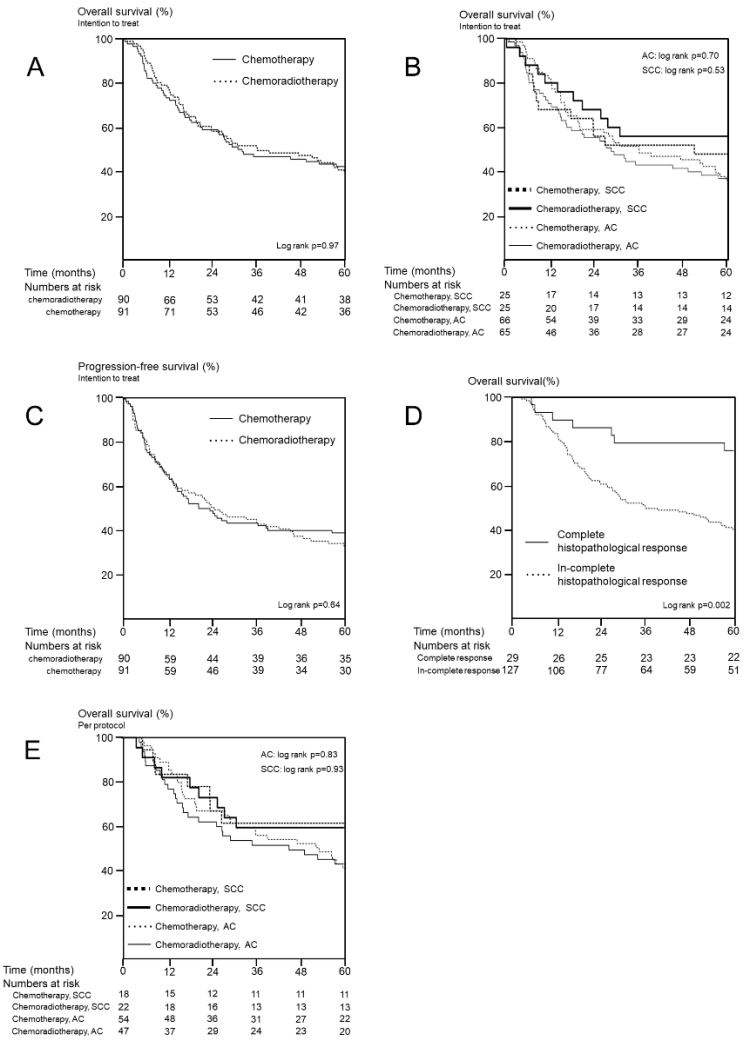

Figure 2 Long-term survival effects of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy followed by surgery for cancer of the esophagus or gastro-esophageal junction.

A Overall survival by treatment group.
Intention to treat.
B Overall survival by treatment group and histology.
Intention to treat.
C Progression-free survival by treatment group.
Intention to treat.
D Overall survival by tumor response
E Overall survival by treatment group and histology.
Per protocol.

Abbreviations:
AC: Adenocarcinoma
SCC: Squamous cell carcinoma

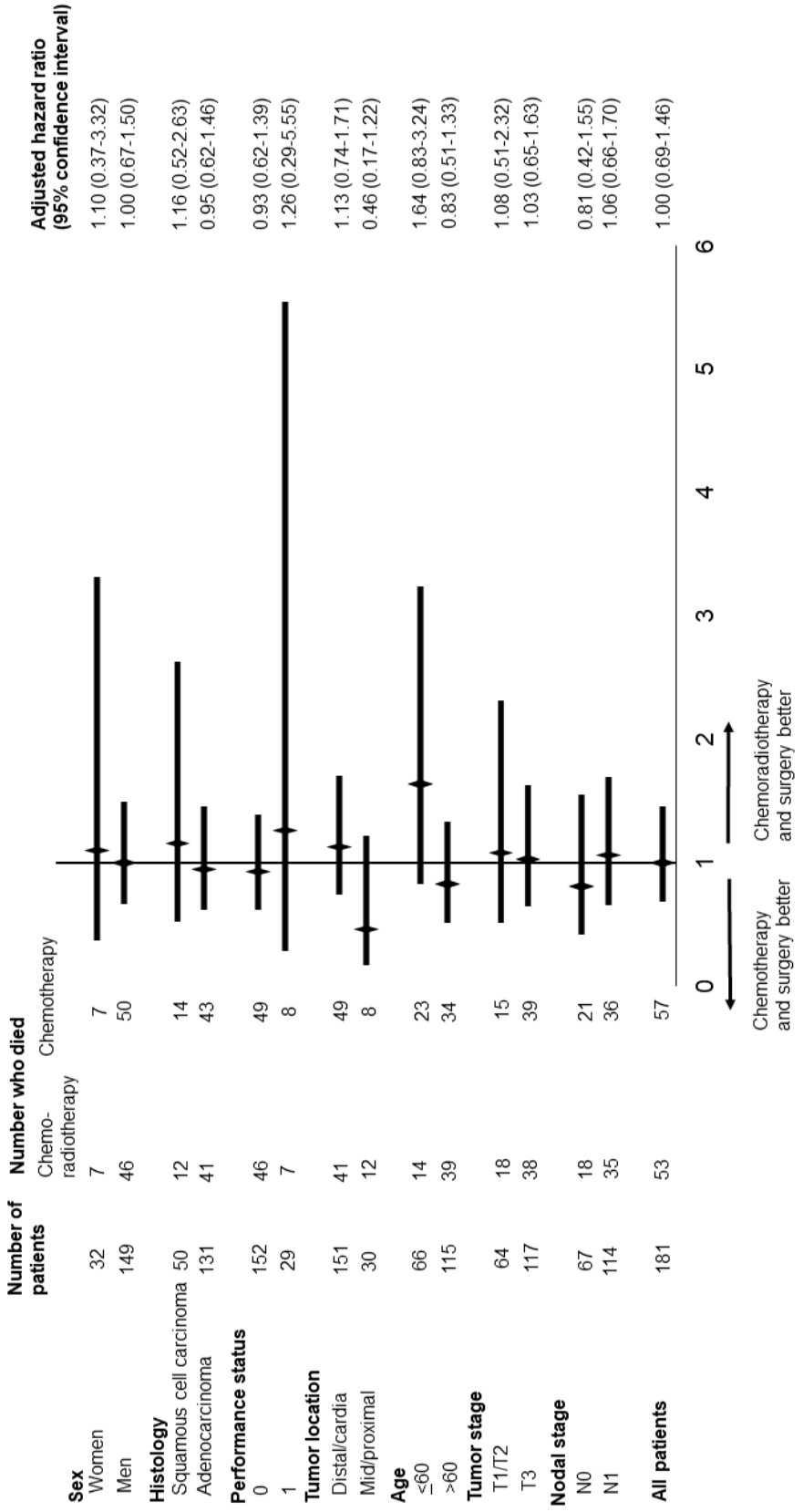

Figure 3 The association between baseline characteristics and overall survival in the two treatment groups.