New insights in optimizing treatment and the role of cancer stem cells in esophageal cancer

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Chapter 3

A comparison of carboplatin and paclitaxel with cisplatinum and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients.

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ABSTRACT

Background: In esophageal cancer (EC) patients who are not eligible for surgery, definitive chemoradiation (dCRT) with curative intent using cisplatinum with 5-fluorouracil (5-FU) is the standard chemotherapy regimen. Nowadays carboplatin / paclitaxel is also often used. In this study we compared survival and toxicity rates between both regimens.

Patients and methods: This multicentre study included 102 patients treated in five centers in the Northeast Netherlands from 1996 till 2008. Forty-seven patients received cisplatinum / 5-FU (75 mg/m2 and 1g/m2) and 55 patients carboplatin / paclitaxel (AUC2 and 50mg/m^2).

Results: Overall survival (OS) was not different between the cisplatinum / 5-FU and carboplatin / paclitaxel group (*P*=0.879, Hazard Ratio [HR] 0.97 confidence interval [CI] 0.62-1.51), with a median survival of 16.1 (CI 11.8-20.5) and 13.8 months (CI 10.8-16.9). Median disease free survival (DFS) was comparable (*P*=0.760, HR 0.93 CI 0.60-1.45) between the cisplatinum / 5-FU group (11.1 months, CI 6.9-15.3) and the carboplatin / paclitaxel group (9.7 months, CI 5.1-14.4). Groups were comparable except clinical T-stage was higher in the carboplatin / paclitaxel group (*P*=0.008). High clinical T-stage (cT4) was not related to OS and DFS in a univariate analysis (*P*=0.250 and *P*=0.201). A higher percentage of patients completed the carboplatin / paclitaxel regimen (82% vs. 57%, *P*=0.010). Hematological and non-hematological toxicity (≥ grade 3) in the carboplatin / paclitaxel group (4% and 18%) was significantly lower than in the cisplatinum / 5-FU (19% and 38%, *P*=0.001).

Conclusions: In this study we showed comparable outcome, in terms of DFS and OS for carboplatin / paclitaxel compared to cisplatinum / 5-FU as dCRT treatment in EC patients. Toxicity rates were lower in the carboplatin / paclitaxel group together with higher treatment compliance. Carboplatin / paclitaxel as an alternative treatment for cisplatinum / 5-FU is a good candidate regimen for further evaluation.

INTRODUCTION

With an increasing incidence and overall 5-year survival of about 15% the prognosis of esophageal cancer (EC) patients remains poor [1-4]. In patients treated surgically with curative intent 5-year survival rates are usually between 25-39%. In an attempt to improve prognosis multimodality treatment has been incorporated during the last two decades. Neoadjuvant chemoradiation has shown to be superior compared to surgery alone with a gain of 12-15%, leading to be the current standard procedure in medically fit patients with curative resectable esophageal carcinoma [5, 6].

In patients who are not eligible for curative intended surgery, due to a close relation of the tumor with- or tethered to vital structures (aorta, trachea, especially the higher lesions) or patients otherwise medically unfit for surgical resection, definitive chemoradiation (dCRT) has to be considered as an alternative option. The RTOG 85-01 trial showed that in patients not receiving surgery, chemoradiation with cisplatinum and 5-fluorouracil (5-FU) improved 5-year survival up to 26% compared to patients receiving only radiotherapy [7, 8]. Several chemotherapy regimens are currently being used as definitive regimen in EC patients. The most commonly used regimens are those consisting of cisplatinum in combination with 5-FU or paclitaxel combined with carboplatin. Current guidelines in the US and Europe recommend the combination of cisplatinum with 5-FU as standard combined with 50.4 Gy radiation therapy [9], while the carboplatin / paclitaxel regimen is frequently used in patients with extensive co-morbidity [10]. Cisplatinum has a high toxicity profile and carboplatin is an often used alternative in platinum-based therapy regimens. However, no study has yet investigated the superiority of one of these regimens in overall survival in patients receiving dCRT.

The aim of this study was to compare the differences in survival and toxicity rates between cisplatinum with 5-FU and carboplatin with paclitaxel as dCRT in a relatively large homogenous cohort of EC patients treated in Northeast Netherlands.

PATIENTS AND METHODS

Patients

In this multicentre retrospective study we analyzed 102 esophageal cancer patients without distant metastases, who were treated with curatively intended dCRT in five centers in the Northeast Netherlands from 1996 till 2008. This subgroup of patients treated with only chemoradiation as definitive treatment is part of a larger cohort

described elsewhere [11]. As described in the publication of Smit et. al. the indications in both dCRT regimens were technically unresectable tumors, medically unfit patients or patient's own choice. Carboplatin / paclitaxel was the standard regimen in two of the five centres and also preferred above cisplatinum/ 5-FU for patients with cardiovascular comorbidity. Patients with other histology than adenocarcinoma or squamous carcinoma were excluded as well as cases with missing relevant staging information or inadequate follow-up.

Methods

Pre-treatment staging

Pre-treatment staging consisted of endoscopic ultrasonography (EUS) with fine needle aspiration (FNA) of suspected lymph nodes, 16-64 multidetector Computed Tomography (md-CT) scans of the neck, chest and abdomen and on indication cervical echographic examination. From 2002 onwards 18-F-fluorodeoxyglucose positron emission tomography (FDG-PET) was added to the staging procedure. Bronchoscopy was required when the tumor was tethered to the trachea or main stem bronchus. Patients were staged according to the Union for International Cancer Control TNM 6th edition [12].

Chemotherapy regimens

The cisplatinum / 5-FU dCRT (*N*=47) regimen consisted of cisplatinum 75 mg/m2 (day 1) and 5-FU 1g/m2 (day 1-4) at week 1 and 5 during radiotherapy (RT), with two additional courses on week 8 and 11 (RTOG 85-01 scheme) [7] .

In the carboplatin/ paclitaxel group (*N*=55) a chemotherapy scheme was given weekly during RT at day 1, 8, 15, 22, 29 (and 35). The paclitaxel dose was 50mg/m^2 and carboplatin was administered at AUC2.

Radiation scheme

Radiotherapy planning was carried out after direct simulation, based on diagnostic images or 3D based on treatment planning CT images. During direct simulation patients had to swallow barium contrast to facilitate identification and localization of the primary tumor. For the planning CT the patients also received oral contrast.

Gross tumor volume (GTV), defined as the macroscopic primary tumor and regional lymph node metastases, was reconstructed using all available information derived from endoscopy, EUS, CT and from FDG-PET.

At direct simulation, margins from GTV to field margin were 5 cm in caudal/cranial

direction and 2 cm margin in transversal plane. A margin of 4 cm in caudal/cranial direction and 1.5 cm in transversal plane was used to generate the planning target volume (PTV). If the treatment planning was based on a planning CT, the clinical target volume (CTV) was obtained by adding a 3 cm margin in cranial-caudal direction and 1 cm margin in transversal plane. A 0.5-1 cm margin was used around pathological lymph nodes.

A total radiation dose of 46.8-70 Gy (median dose 50.4Gy) was given in daily fractions of 1.8-2 Gy. One patient received a dose of 41.1Gy as the initial neoadjuvant treatment was switched to dCRT. Generally delivered with at least 6 MV photons. Intra luminal brachytherapy (ILBT) given in 2 fractions of 6 Gy or a single fraction of 10 Gy and was administered in 5% of the patients.

Data acquisition

Data was obtained using the medical records of the different centers in the North-East region of the Netherlands. Additional information from comprehensive cancer centers was acquired. The study was performed according to national ethics guidelines (www.ccmo-online.nl).

Follow-up

Patients were generally seen for regular follow up according to national guidelines at 4 to 8 weeks after completion of treatment, every 6 months in the first year and thereafter annually up to 5 years or until death.

Toxicity

Toxicity was measured according to the Common Terminology Criteria for Adverse Events (CTCAE 4.0). Grade 3 and 4 toxicity reactions are shown in table 3. Grade 5 toxicity occurring up to 30 days after treatment was recorded as mortality.

Statistics

Overall survival (OS) was defined as the time interval between the starting date of the chemoradiation and documentation of the day of death or last follow-up. Disease-free survival (DFS) was determined from the starting date of treatment to documented date of first recurrence or death of any cause. OS and DFS rates were calculated according to the Kaplan-Meier method and compared using the log-rank test. Patient characteristics and toxicity rates were determined and compared using Student t-test and Fisher's exact test. Univariate and multivariate analyses were performed using Cox-regression analyses. *P* values < 0.150 in the univariate analysis

were included in the multivariate analysis. A *P* value <0.05 (95% confidence interval [CI]) was considered as significant. The statistical analyses were performed by using the Statistical Package for Social Sciences (SPSS, Chicago IL, USA) version 18.0 software.

RESULTS

Patient and tumor characteristics

Patient characteristics are shown in table 1. Age (*P*=0.169), sex (*P*=0.468) and WHO-performance (*P*=0.334) did not differ among both groups. In both groups comorbidity was equally present, 49% in the cisplatinum / 5-FU group and 55% in the carboplatin / paclitaxel group (*P*=0.691). The type of comorbidity varied between the groups as the carboplatin / paclitaxel group had more cardiovascular and pulmonary comorbidity (38%) compared to the cisplatinum / 5-FU group (19%, *P*=0.049). Of the tumor characteristics, localization differed with more gastro-esophageal junction (GEJ) tumors in the cisplatinum with 5-FU group (*P*=0.05). Clinical T-stage did differ (*P*=0.008) with a T3 stadium of 67% in the cisplatinum / 5-FU group, while the majority of patients in the carboplatin / paclitaxel group (55%) had a higher stage group T4. N-stage (*P*=0.465) was comparable between both groups. A higher percentage of patients in the cisplatinum with 5-FU group had a cM1a stage (23%) compared to the paclitaxel with carboplatin group which was not significant (9%, *P*=0.061). Most patients received a radiation dose of 50-50.4 Gy in both treatment groups and the distribution of radiation dose did not differ between the hospitals (*P*=0.181).

Overall Survival and Disease Free Survival

Overall Survival (OS) was comparable between the cisplatinum with 5-FU group and the carboplatin with paclitaxel group (*P*=0.879, HR 0.97 CI 0.62-1.51), with a median survival of respectively 16.1 (CI 11.8-20.5) and 13.8 (CI 10.8-16.9) months (figure 1.a). Disease free survival (DFS) was also not significantly different (*P*=0.76, HR 0.93 CI 0.60-1.45). Median DFS was 11.1 in the cisplatinum with 5-FU group (figure 1.b, CI 6.9-15.3) and 9.7 months with carboplatin with paclitaxel (CI 5.1-14.4). OS and DFS were also not different between both chemotherapy regimens when analyzed for the two histological subtypes adenocarcinoma and squamous cell carcinoma (Supplementary figure S1). As the Kaplan-Meier survival curves cross the proportional hazards criterion for the logrank test is not met. Therefore we also tested smaller groups (OS and DFS 24 months) in the ESCC group for both regimens and found they were not significant (data not shown).

Table 1: Clinical and patient characteristics.

	Cisplatinum / 5-FU (*N* =47)	Carboplatin / Paclitaxel (*N* =55)	*P*-value
Age (mean, years)	62.5	64.8	0.169#
Sex (m/f)	39 (83%) / 8 (17%)	42 (76%) / 13 (24%)	0.468
cT1	0 (0%)	1/47 (2%)	*0.008*
cT2	3/46 (7%)	2/47 (4%)	
cT3	31/46 (67%)	18/47 (38%)	
cT4	12/46 (26%)	26/47 (55%)	
cN1 (%)	39/47 (83%)	41/54 (76%)	0.465
cM1a (%)	11/47 (23%)	5/54 (9%)	0.061
Histology (AC/SCC)	28 (60%) / 19 (40%)	23 (42%) / 32 (58%)	0.112
Tumor length >5cm	25/36 (69%)	27/38 (71%)	1.000
Tumor site			*0.050*
Upper	9/44 (21%)	14/54 (26%)	
Mid	4/44 (9%)	10/54 (19%)	
Distal	22/44 (50%)	28/54 (52%)	
GEJ	9/44 (21%)	2/54 (4%)	
WHO performance			0.334
0-1	45/47 (96%)	47/54 (87%)	
2	2/47 (4%)	5/54 (9%)	
3	0 (0%)	2/54 (4%)	
Radiation dose			0.062
<50.0 Gy	1 (2%)	2 (4%)	
50.0-50.4 Gy	42 (89%)	53 (96%)	
>50.4 Gy	4 (9%)	0 (0%)	
Comorbidity present	23/47 (49%)	30/55 (55%)	0.691
Cardiovascular and pulmonary comorbidity	9/47 (19%)	21/55 (38%)	*0.049*
Type of comorbidity			*0.048*
None	24/47 (51%)	25/55 (46%)	
Pulmonary	1/47 (2%)	9/55 (16%)	
Cardiovascular	8/47 (17%)	12/55 (22%)	
Other	14/47 (30%)	9/55 (16%)	

Student t-test, all other variables were compared using a Fisher's exact test. GEJ, gastroesophageal junction.TNM classification according to sixth edition. *P*< 0.05 was considered significant, significant values presented in italics

Univariate and Multivariate Cox-regression analysis

Chemotherapy regimen was not related to OS and DFS in an univariate analysis (HR=0.97, *P*= 0.879 and HR=0.93, *P*=0.760). Other factors as comorbidity, localization and completion of the chemotherapy were significantly related to OS (Supplementary table S2, *P*=0.031, *P*=0.028 and *P*=0.046). Comorbidity, tumor localization, cN-stage and completion of chemotherapy were related to DFS (*P*=0.107, *P*=0.014, *P*=0.114, *P*=0.123). When corrected for these factors in a multivariate Cox-regression analysis OS and DFS did not change drastically for chemotherapy regimen (table 2, *P*= 0.990 HR 1.00, CI 0.61-1.64 and *P*= 0.641 HR 0.89, CI 0.54-1.47). None of the other factors was an independent prognostic factor for OS or DFS.

a. b.

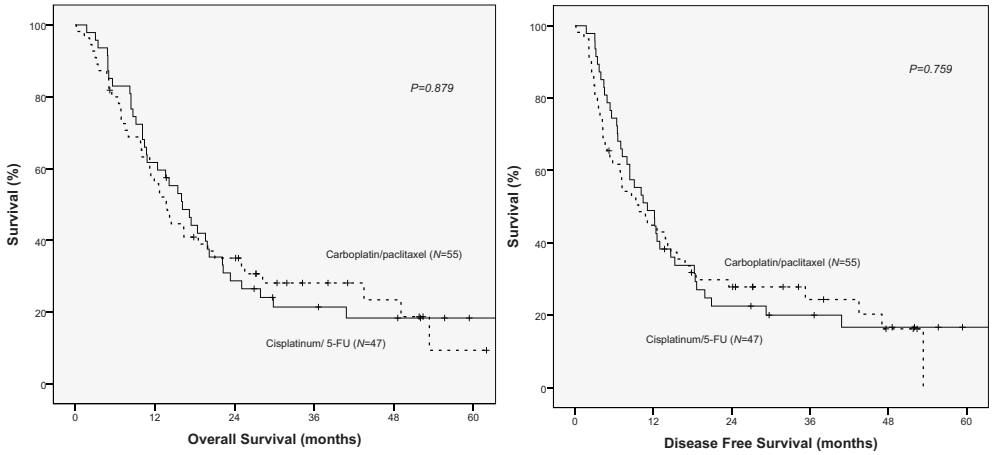

Figure 1: Kaplan-Meier survivals estimation of the Overall Survival (a) and Disease Free Survival (b) for dCRT with cisplatinum/5-FU (*N*=47) or carboplatin /paclitaxel (*N*=55).

Table 2: Multivariate Cox-regression analysis.

Multivariate analysis	*HR*	(95% CI)	*P-value*
OS (N=97)			
Chemotherapy regimen	1.00	(0.61-1.64)	0.990
Comorbidity present[a]	0.67	(0.39-1.13)	0.135
Localization			0.149
Upper	0.62	(0.25-1.57)	0.314
Mid	1.49	(0.57-3.87)	0.418
Distal	1.20	(0.52-2.75)	0.669
GEJ	Reference		
Completed chemotherapy	1.28	(0.73-2.24)	0.388
DFS (*N*=96)			
Chemotherapy regimen	0.89	(0.54-1.47)	0.641
Comorbidity present	0.78	(0.46-1.32)	0.357
cN	0.63	(0.32-1.22)	0.168
Localization			0.301
Upper	0.90	(0.35-2.34)	0.829
Mid	1.61	(0.62-4.16)	0.330
Distal	1.59	(0.70-3.65)	0.270
GEJ	Reference		
Completed chemotherapy	1.45	(0.82-2.56)	0.198

[a]Due to the large number of subgroups comorbidity was only included as dichotomous variable. GEJ, gastroesophageal junction

Toxicity and Mortality

Table 3 shows the treatment compliance and toxicity grades. A higher percentage of patients with carboplatin / paclitaxel completed their treatment compared with the cisplatinum / 5-FU group (82% vs 57%, *P*=0.010). The occurrence of side-events was significantly lower in the carboplatin / paclitaxel group compared with the cisplatinum / 5-FU group (*P*=0.001). In the cisplatinum / 5-FU group 38% (*N*=18/47) experienced a grade 3 toxicity and 15% (*N*=7/47) a grade 4 toxicity. In the carboplatin / paclitaxel group treated patients toxicity rates were lower, 15% (*N* =8/55) experienced a grade 3 toxicity and 6% (*N*=3/55) a grade 4 toxicity. Hematologic toxicity was most common and higher in the cisplatinum / 5-FU group (19% versus 4%, *P*=0.021). Non-hematologic adverse events were also more common in the cisplatinum / 5-FU group (38% versus 18%, *P*=0.028).

In the cisplatinum / 5-FU group two patients died due to treatment related events. One patient had atrial fibrillation resulting in brain infarction and death. The other patient developed severe bone marrow depletion and died from neutropenic sepsis based on a pneumonia. In the carboplatin / paclitaxel group one patient with previous hepatocellular carcinoma died due to liver failure and severe diarrhea.

Table 3: Treatment compliance and major toxicities.

	Cisplatinum / 5-FU (*N* =47)	Carboplatin / Paclitaxel (*N* =55)	*P*-value
Completed chemotherapy	27 (57%)	44 (82%)	*0.010*
Toxities (CTCAE 4.0)			
overall toxicity (≥ gr3)	26[a] (55%)	12 (22%)	*0.001*
Hematological ≥gr3	9 (19%)	2 (4%)	*0.021*
Non-hematological ≥gr3	18 (38%)	10 (18%)	*0.028*
Gr3	18 (38%)	8 (15%)	*0.011*
Gr4	7 (15%)	3 (6%)	0.180
Mortality	2 (4%)	1 (2%)	0.594
Hematologic**			
Febrile leucopenia	6 (13%)	2 (4%)	0.139
Trombocytopenia	1 (2%)	2 (4%)	1.000
Bleeding	1 (2%)	0 (0%)	0.461
Anemia	3 (6%)	3 (6%)	1.000
Non-Hematologic[b]			
Nauseau/Vomiting	2 (4%)	0 (0%)	0.210
Fatigue	1 (2%)	0 (0%)	0.461
Diarrhea	0 (0%)	1 (2%)	1.000
Mucositis	2 (4%)	2 (4%)	1.000
Other	14 (30%)	7 (13%)	0.049

Compared using Fisher's exact test. [a] In cisplatinum / 5-FU group one patient had both a grade 3 hematological toxicity as a grade 4 non-hematological toxicity. [b] All recorded toxicity. *P*< 0.05 was considered significant, significant values presented in italics.

DISCUSSION

In this study we described comparable outcomes in terms of OS and DFS between EC patients treated with cisplatinum / 5-FU and with carboplatin / paclitaxel as part of dCRT. Severe toxicity rates including hematological and non-hematological events (both ≥ grade 3) were significantly lower for the carboplatin / paclitaxel group (*P*=0.001). Furthermore, a significantly higher percentage of patients completed their therapy in the carboplatin with paclitaxel group which could be due to fewer and milder adverse events (*P*=0.010). However completion of chemotherapy was not an independent prognostic factor for OS or DFS in a multivariate analysis.

Literature concerning the effectiveness and side effects of carboplatin with paclitaxel compared with standard cisplatinum with 5-FU is limited. Supplementary table S3 gives an overview of the literature reporting on one or both of the schemes in dCRT in EC. Polee et al. were the first to show the use of carboplatin with paclitaxel as dCRT scheme in a phase I study [13]. Median survival was 11 months and myelotoxicity was regarded acceptable as only 5% of the 77% with neutropenia developed fever. Wang et al. showed a good response rate in a small group of EC patients with locally advanced disease (*N* =16) treated with dCRT with carboplatin and paclitaxel with an overall 3-year survival rate of 60% [14] . However, they do not compare this regimen with other chemotherapy regimens. Courrech Staal et al. compared carboplatin with paclitaxel and cisplatinum with 5-FU, in both a curative dCRT and a neoadjuvant setting [15] . The median OS was 15 months for the dCRT group (*N* =49), which is similar as to our study. No survival distinction was made between the two therapy regimens in this study. A recent study of Blom et al. compared cisplatinum/ 5-FU and carboplatin/ paclitaxel in the neoadjuvant setting in EC patients and showed comparable overall toxicity (≥grade 3) as in our study and no difference in survival [16].

Toxicity rates for the carboplatin with paclitaxel group of our study were comparable to the rates in the CROSS-trial. In our study 4% of patients experienced hematological events (≥ grade 3) and 18% non-hematological events (≥grade 3) compared to 7.6% and 13%, respectively in the CROSS-trial [6] .

Our study is limited by the number of patients included and the retrospective design. An important limitation is that patients were not randomized, which could lead to differences in patient characteristics and treatment per hospital between both treatment groups. Between our groups we showed no differences in outcome but a larger number of patients would be required to make these conclusions more robust.

A fase III trial would be suitable for that purpose. However, the number of EC patients receiving dCRT is limited and we do not expect groups to become significant with larger numbers. As toxicity rates are lower in the carboplatin / paclitaxel group an evaluation of the quality of life would also be of interest in future studies.

Another important difference between our groups is that patients in the carboplatin / paclitaxel group had more cardiovascular and pulmonary comorbidity. This could suggest a possible selection bias to include patients in better physical condition in the cisplatinum / 5-FU group. However, most patients (78%) receiving carboplatin / paclitaxel were treated in the two centres were this was the standard regimen thereby arguing against a selection bias.

In conclusion, the present study suggests that OS and DFS are similar in both treatment regimens in dCRT in esophageal cancer. Carboplatin with paclitaxel has fewer adverse events with higher treatment compliance. These results suggests carboplatin /paclitaxel could be used as an alternative for cisplatinum / 5-FU in dCRT for esophageal cancer patients which should be further evaluated.

DISCLOSURE

The authors have declared no conflicts of interest

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SUPPLEMENTARY MATERIAL

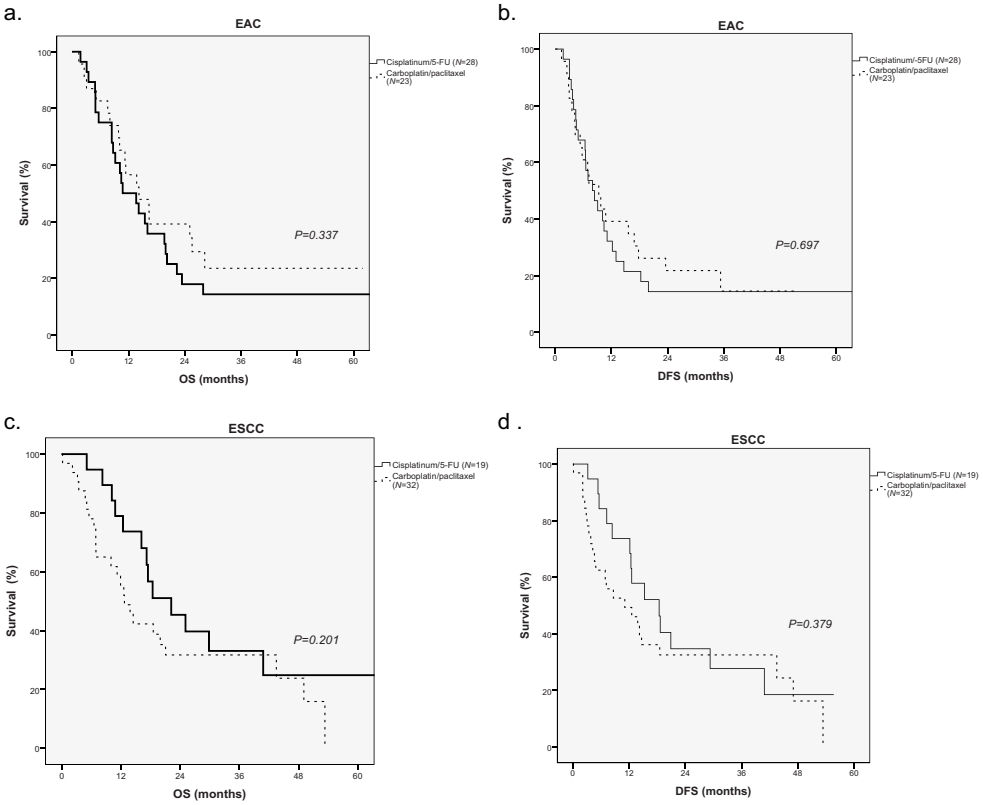

Figure S1: Overall Survival (OS) and Disease Free Survival (DFS) in patients with esophageal adenocarcinoma (EAC) and patients with esophageal squamous cell carcinoma (ESCC) for dCRT with cisplatinum with 5-FU or carboplatin with paclitaxel. a) OS in EAC, b) DFS in EAC, c) OS in ESCC and d) DFS in ESCC.

Table S2: Univariate analysis

Univariate analysis	OS (*N*=97)			DFS (*N*=96)		
	HR	(95% CI)	*P-value*	HR	(95% CI)	*P-value*
Chemotherapy regimen	0.97	(0.62-1.51)	0.879	0.93	(0.60-1.45)	0.760
Sex	1.30	(0.74-2.29)	0.356	1.47	(0.84-2.58)	0.178
Comorbidity present	0.61	(0.39-0.96)	0.031*	0.70	(0.47-1.08)	0.107*
WHO			0.768			0.777
0-1	1.38	(0.19-9.98)	0.750	1.97	(0.27-14.25)	0.500
2	1.81	(0.22-15.12)	0.584	2.11	(0.25-17.58)	0.490
3	Reference			Reference		
Localization			0.028*			0.014*
Upper	0.69	(0.29-1.67)	0.413	0.74	(0.31-1.78)	0.499
Mid	2.02	(0.83-4.89)	0.120	2.18	(0.90-5.30)	0.085
Distal	1.46	(0.68-3.11)	0.332	1.70	(0.80-3.62)	0.169
GEJ	Reference			Reference		
cT #	0.76	(0.48-1.21)	0.250	0.74	(0.47-1.17)	0.201
cN	0.77	(0.44-1.35)	0.360	0.64	(0.36-1.12)	0.114*
cM	1.01	(0.54-1.88)	0.974	0.97	(0.54-1.76)	0.917
Histology	1.21	(0.78-1.89)	0.400	1.37	(0.88-2.12)	0.159
Age	1.00	(0.97-1.03)	0.946	1.00	(0.98-1.03)	0.867
Completed chemotherapy	1.60	(1.00-2.57)	0.046*	1.44	(0.90-2.29)	0.123*

* Variables with a *P*<0.150 were included in the multivariate analysis. # cT-stage was divided into two groups cT1-T3 and cT4.

Table S3: Literature overview of articles concerning 5-FU and cisplatinum or carboplatin and paclitaxel in the curative setting.

Reference	*N*	*Histology*	*Regimen*		*Respons*	*Survival*	*Toxicity gr 3-4*				*Mortality*
			Chemotherapy	Radiotherapy			Hematological		Non-hemato-logical		
							3	4	3	4	
Wang#[[14]	50	SCC:16 EAC:34	Paclitaxel 30 mg/ m2 10-11 doses carboplatin 1.5mg/ ml/min 5-6 doses Consolidation therapy for non-surgical patients: an extra 2x paclitaxel 200mg/m2 and carboplatin AUC6	Surgical patiënts total 45Gy. Non-surgical 50,4 Gy	12% complete 8% partial 19% stable 9% progressive 41% dysfagie relief	3-year survival 60% local + no surgery(n=16) 60% local + surgery (n=8) 14% metastatic disease (n=20)	9 (7)		6 (3)	0	
Polee[13]	40	SCC:5 EAC:34 Undiff:1	Paclitaxel 100mg/m2 Carboplatin AUC 2-5mg min/ml		Partial 19 (51%) Complete: 1 (with additional RT 50Gy) Stable 10 (27%) Progressive 7 (18%)	1yr 46% Median survival 11 months	Neutropenia Gr 3-4 in 25 (77%) Trombocytopenia Gr 3-4 in 4 (10%) Anemia Gr 3-4 in 0		2	0	
Courrech Staal*[15]	94	SCC 43 EAC 46 Adenosquamous 5	A (n=65): cis 75 mg/ m2 + 5-FU 800 mg/ m2 B (n=16): carboplatin 2 AUC + paclitaxel 50 mg/m2 6 times C (n=13): cis platin low dose 6 mg/m2 Total 41 surgery afterwards	A: 50 Gy B: 50.4 Gy C: 66 Gy	Complete or partial response overall: 30% A 21% B 50% C 54%	OS 1 3 year A 65 41 B 88 55 C 76 19 T 70 41 Chemoradio+surgery 1yr 79% 3yr 61% Definitive chemoradition 1yr 63% 3yr 24%	A:8 B:9 C:1	A:9 B:0 C:0	A: 8 B: 0 C: 3	A:0 B:0 C:0	
Herkovic** (RTOG trial) [8]	121	SCC 106 EAC 15	A: (n=61) cis platin 75 mg/m2 4 times + 5-FU1g/m2 16 times B: (n=60) radiotherapy alone	A: 50Gy B: 64Gy	Recurrence: 1) within RT field A 39% B 52% 2) distant metastasis A 7% B 13% 3) within field+metastasis A 5% B 13% 4) death of disease A 7% B 5%	1yr survival A 50% B 33% Combined 2yr A 36% B 10% Median survival A 12,5 months B 8.9 months	A: 20 B: 2	A: 8 B: 0	A: 29 B:14	A:7 B: 2	A:1 B:0

Cooper## (RTOG trial 85-01)[7]	123 randomized 69 non-randomized	SCC 107 EAC 23	A: cisplatin 75 mg/m2 4 times + fluorouracil 1g/m2 16 times B: radiotherapy alone	A: 50Gy B: 64Gy	8yr followup Complete: A 27% B 0%, Persistent: A 26% B 18% Local regional disease: A 17% B 16% Distant only: A 12% B 15% Local,regional and distant: A 9% B 15% Death: A 22.3% B 18%	5yr survival: A 26% B 0%				A:1(2%) B: 0 (0%)
EL-Rayes***[17]	15 non metastatic 20 metastatic	SCC 13 EAC 22	Paclitaxel 200mg/m2 Carboplatin AUC of 5mg/h/ml Median 5 courses (range 1-12)		15 partial response (45%) nonmetastatic 33% metastatic 50%	1yr 43% 2yr 17% Median survival 9 months	17	8	14	0
Ruppert*#[18]	19	SCC 8 EAC 11	Paclitaxel 30-50 mg/m2 2x weekly and carboplatin AUC2 weekly during RT, followed by carboplatin 6AUC and paclitaxel 175-200mg/m2 for 2 cycles given every 3 weeks	50.4 to 61.2 Gy	8 complete response 2 partial	3yr 56%	5	5	4	0

* Within these groups 41 patients underwent surgery after chemoradiation, not further specified per group.
** Toxicity was scored as severe and life-treatening
*** In the non-metastatic group 3 patients had surgery
# grade 3 and 4 events combined, between brackets toxicity after consolidation therapy
Unspecified: RT alone:gr 3 10(19%), gr4 2 (4%) Randomized group combined therapy: gr3 13(25%), gr4 2(4%) Nonrandomized combined: Gr3 15(23%), gr4 2(3%), gr5 1(2%)
*# Six patients underwent surgery afterwards