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Survival Outcomes and Toxicity of Concurrent Chemoradiotherapy for Esophageal Cancer

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ABSTRACT

Aims: The aim of the study was to investigate the impact of chemoradiotherapy(CRT) on survival of patients with unresectable esophageal cancer treated with radiotherapy combined with either concurrent DCF [docetaxel, cisplatin +5-fluorouracil(5-FU)] or CF [cisplatin and 5-FU).Patients and methods:Data of patients who underwent CRT for esophageal cancer during 2010 and 2015 in the department of Clinical Oncology, Assiut University Hospital, Egypt were collected. Patients received either CF every 4-week, cisplatin (75 mg/m2) on day 1 followed by 5-fluorouracil (5-FU) 1000 mg/m2/24 h IV on days 1-4 for 4 cycles or DCF as IV infusions of docetaxel (40 mg/m2), cisplatin (40 mg/m2) on day 1 and 5-FU (400 mg/m2/day) on days 1 to 5, every 2 weeks for 3 cycles. Both groups received 50 Gy of radiotherapy in 25 fractions.Results: We identified 51 patients. The mean progression-free survival (PFS) and overall survival (OS) of the cohort were 19.83 and 29.30 months respectively. Improved OS was achieved with stratification according to T3/N+/stage III with DCF (20 patients) in comparison with CF (31 patients). Grade 3-4 leucopoenia (22.6% vs. 60.6%) and febrile neutropenia (16% vs. 30%) were significantly higher in DCF groupConclusions:Our data suggest that CRT has a role in improving survival of patients with esophageal cancer. DCF therapy compared with CF improved OS in locally advanced esophageal cancer patients.

INTRODUCTION

Esophageal cancer (EC) is the eighth common cancer in the world and the sixth cause of death from cancer worldwide [1, 2].The incidence of EC is more in less developed and developing countries[3].

Chemoradiotherapy for stage II–IIIesophageal cancer, showed a completeresponse rate of 62.2% and 5-year survival of36.8%[4].

The common radiosensitizers in EC iscisplatin and 5-fluorouracil. However, the outcomes of this regimen remain unsatisfactory[5].Studies have reported encouraging results for docetaxel and cisplatinin EC and radiotherapy[6, 7].

The aim of this study was to investigate the impact of concurrent chemoradiation on survival of patients withlocoregionalesophageal cancer retrospectively and to compare the efficacy and toxicities of cisplatin+ 5-fluorouracil versus docetaxel, cisplatin and 5-fluorouracil regimens.

Patients and methods

In this observational study, the medical record of patients diagnosed withunresectable thoracic esophageal cancer who received concurrent chemoradiotherapyas a primary treatment with either cisplatin-5-fluorouracil (CF) or docetaxel-cisplatin-5-fluorouracil (DCF),at Clinical Oncology department, Assiut University Hospital, Egypt between January 2010 and December 2015 were retrospectively reviewed.

Study eligibility included patients with biopsy-proven esophageal cancer (squamous cell carcinoma or adenocarcinoma), stage II or III according to the American Joint Committee on Cancer (AJCC)[8] staging system 7th edition with Easter Cooperative Oncology Group performance status ≤2.

Exclusion criteria included patients treated with other concurrent chemoradiotherapy regimen, patients who received induction chemotherapy and patients with distant metastases.

The protocol of the study was approved by the ethics committee of Assiut University, Egypt before the study was activated. The treatment was applied in accordance with the Declaration of Helsinki with a written informed consent was obtained from all patients.

Radiotherapy and chemotherapy

In the PF group, two cycles of 5-fluorouracil and cisplatin were given during radiotherapy at 4-week intervals. 2-hour infusion of cisplatin (75 mg/m^2) was administered on day 1 with standard hydration, followed by 5-fluorouracil 1000 mg/m^2/24 h by continuous intravenous infusion on days 1-4 of each cycle. Patients had a 4-week rest after the completion of radiation and then received an additional two cycles of chemotherapy.

Patients who had T3 tumor or lymph node metastases that were diagnosed between 2014 and 2015 received DCF combination regimen. Patients received intravenous infusions of docetaxel (40 mg/m^2) and cisplatin (40 mg/m^2) on day 1 and a continuous intravenous infusion of 5-fluorouracil (400 mg/m^2/day) on days 1 to 5, every 2 weeks, plusconcurrentradiation for 3 cycles.

Radiotherapy was started on day 1 concomitantly with chemotherapy in both groups. Thesuperior and inferior extent of the tumor was defined by simulator with barium swallow. The length of the target volume was chosen to allow a 5 cm margin superior and inferior to tumor limits and 2 cm lateral marginwas used to include soft tissue disease in the esophageal wall.

Radiotherapy was delivered with linear accelerator (6 MV) or cobalt-60 machines to a doseof 45Gy, 2Gy/fraction, 5 fractions per week over 4.5 weeks by anterior and posterior opposing fields. Two-dimensional treatment planning was used.

Assessment

Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors, version 1.0[9] with endoscopy and computed tomography (CT) performed afterchemoradiation course to assess response. CT and endoscopy were repeated every 3 months during the first year, every 4 months in the second year and every 6 months thereafter. The date of last follow-up was December 2016.

Acute toxicities were assessed weekly during CRT and every 3 weeks after CRT completion. The toxicities were evaluated basedon the Common Terminology Criteria for Adverse Events (Version 4.0)[10].

Statistical analysis

The outcome measurements of this study included overall survival, progression-free survival and response rate. The response rate was defined as complete response or partial response. Progression-free survival (PFS) was defined as the time from the first day of treatment to the first observation of disease progression or death as a result of any cause. Overall survival (OS) was defined as the time from the first day of treatment to the time of death as a result of any cause, censored at the last date known alive.

Data expressed as number, percentage, mean ± Standard error and median. Chi square test was used to determine significance of percentage variables. Student T-test was used to determine significance comparison of means and medians. The median survival and PFS time were estimated with the Kaplan-Meier method and compared with Log-rank test. A P value <0.05 was considered statistically significant. All data were analyzed using SPSS software (version 18.0, Chicago-IL).

RESULTS

Fifty-one patients were eligible and included in the study. There were no statistical significant differences between the two arms (CF arm and DCF arm) as regard patients and tumor characteristics as shown in Table 1.

Table 1: Clinical data of patients with esophageal cancer

Variables	**All patients N=51 (%)**	**Arm 1 (CF*) N=31.(%)**	**Arm2(DCF†) N=20 (%)**	**P value**
Age, median "years"	60.0			
Range	(29.0-78.0)			
Sex:				
Female	26(51.0%)	15(48.4%)	11(55.0%)	0.431
Male	25(49.0%)	16(51.6%)	9(45.0%)	
ECOG PS╪:				
0	30(58.9%)	17(54.83%)	13(65.0%)	0.102
1	15(29.4%)	8(25.80%)	7(35.0%)	
2	6(11.8%)	6(19.35%)	0.0	
T stage:				
T2	9(17.6%)	7(22.6%)	2(10.0%)	0.360
T3	35(68.6%)	19(61.3%)	16(80.0%)	
T4	7(13.7%)	5(16.1%)	2(10.0%)	
N stage:				
N0	6(11.8%)	5(16.1%)	1(5.0%)	0.214
N+	45(88.2%)	26(83.9%)	19(95.0%)	
Clinical stage:				
Stage II	12(23.5%)	9(29.0%)	3(15.0%)	0.209
Stage III	39(76.5%)	22(71.0%)	17(85.0%)	
Tumor Location:				
Upper third	33(64.7%)	5(16.1%)	1(5.0%)	0.393
Middle third	12(23.5%)	6(19.4%)	6(30.0%)	
Lower third	6(11.8%)	20(64.5%)	13(65.0%)	
Histology:				
Adenocarcinoma	35(68.6%)	21(67.7%)	14(70.0%)	0.556
Squamous cell carcinoma	16(31.4%)	10(32.3%)	6(30.0%)	

Abbreviations: CF= cisplatin+ 5-fluorouracil, DCF†= docetaxel+ cisplatin+ 5-fluorouracil, ECOG, PS╪= Eastern Cooperative Oncology Group performance status*

The mean PFS of the study cohort was 19.83 months ±1.27 (95% confidence interval 17.29-22.38). The overall response rate (complete response and partial response) of all patients treated with concurrent chemoradiation was 47%. There was no significant difference in response rate between 2 arms (Table 2).

Table 2: Response of patients with esophageal cancer underwent chemoradiotherapy

Response	All patients N (%)	Arm 1 (CF*), N (%)	Arm 2(DCF†) N (%)	P value
-Complete response (CR)	4(7.8%)	2(6.5%)	2(10.0%)	
-Partial response (PR)	20(39.2%)	9(29.0%)	11(55.0%)	
-Overall response (CR+PR)	**24(47.0%)**	**11(35.5%)**	**13(65.0%)**	.162
-Stable disease	16(31.4%)	13(41.9%)	3(15.0%)	
-Progressive disease	11(21.6%)	7(22.6%)	4(20.0%)	

Abbreviations: CF= cisplatin+ 5-fluorouracil, DCF†= docetaxel+ cisplatin+ 5-fluorouracil*

Patients with T3, N+ and stage III had a better survival when treated with DCF. Factors associated with OS of patients stratified by treatment (CF vs. DCF) are shown in Table 3.

Table 3: Factors affecting survival of patients with esophageal cancer treated by CF* versus DCF†

Factor	N of patients	Arm 1 (CF) median OS╪ (95%CI§)	Arm2 (DCF) median OS (95%CI)	P value
T stage				
T3	35	11.0(9.35-12.64)	16.0(10.77-21.22)	0.04
T4	7	5.00(.85-5.14)	5.00(2.85-7.14)	1
N stage				
N+	45	9.00(7.30-10.69)	13.04(10.02-21.97)	0.04
TNM stage				
Stage II	12	11.0(5.15-16.84)	12.00(5.59-18.40)	0.857
Stage III	39	5.00(3.16-6.83)	10.00(8.06-11.93)	0.001

Abbreviations: CF= cisplatin+ 5-fluorouracil, DCF†= docetaxel+ cisplatin+ 5-fluorouracil, OS╪= overall survival, 95% CI§= confidence interval*

Grade 3-4 leucopoenia and febrile neutropenia and were more common in the DCF arm than the CF. No treatment-related deaths were observed. Toxicity is shown in Table 4.

Table 4: Acute toxicity (CTC AE* Version 4.0) of chemoradiotherapy for esophageal cancer

Toxicity ≥Grade 3	All patients N=51 (%)	Arm 1 (CF†) N= 31(%)	Arm2 (DCF╪) N=20 (%)	P value
-Leucopoenia	21 (41.17)	7 (22.58)	14(66.66)	0.001
-Febrile neutropenia	11 (21.56)	5 (16.12)	6 (30.0)	0.01
-Anemia	5 (9.80)	2 (6.45)	3 (14.28)	0.394
-Thrombocytopenia	3 (5.88)	1 (3.22)	2 (9.52)	0.605
-Esophagitis	10 (19.60)	5 (16.12)	5 (23.80)	0.219

Abbreviations:,CTC-AE Version 4.0, Common Terminology Criteria for Adverse EventsVersion 4.0, CF†= cisplatin and 5-fluorouracil, DCF╪= docetaxel, cisplatin and 5-fluorouracil*

Kaplan-Meier estimate of OS time of the study cohort was presented in Figure 1.

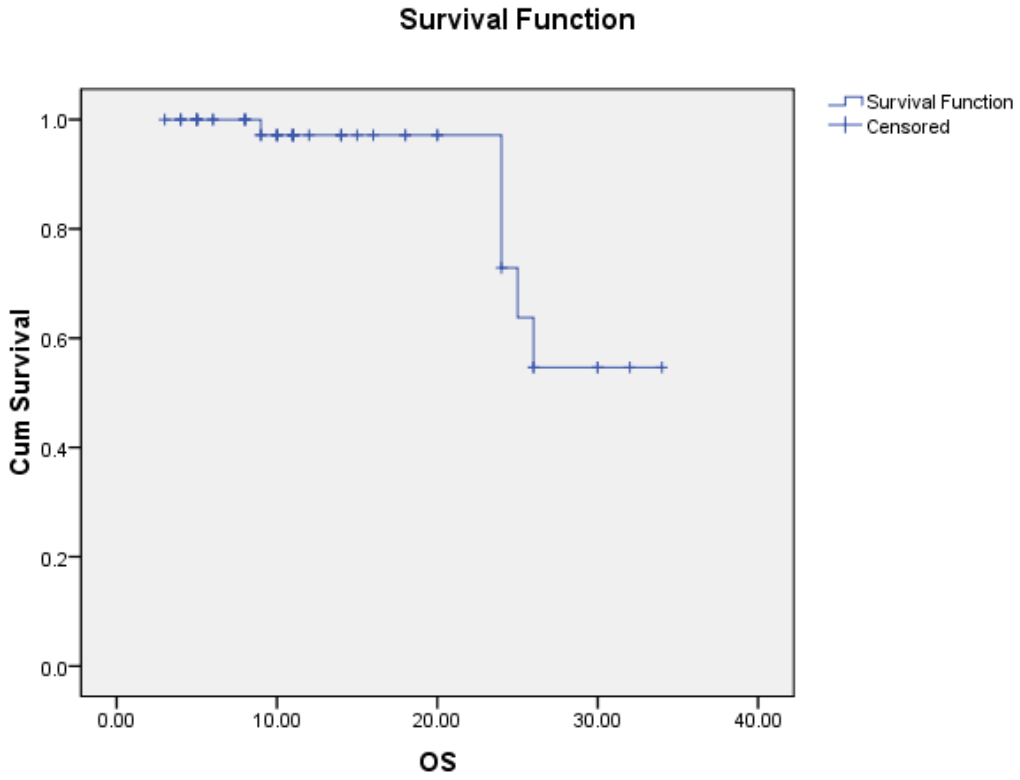

Figure 1: Overall survival (OS) of patients with esophageal cancer treated with chemoradiation, mean OS=29.30 ± 1.47 months, 95% confidence interval 26.42-32.19

Analysis of OS of CF and DCF arms was demonstrated in Figure 2.

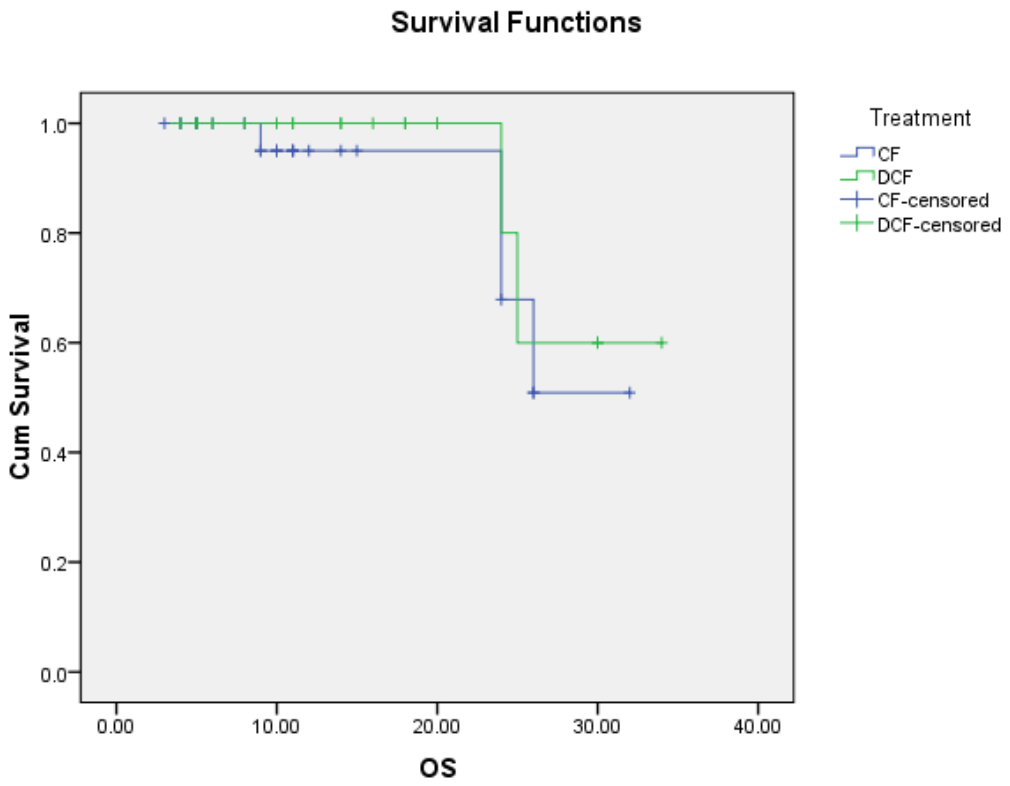

Figure 2: Overall survival (OS) of patients with esophageal cancer treated with chemoradiation, mean OS of DCF = 30.20±2.08 months, 95% confidence interval (CI) 26.11-34.28, OS of CF=27.66±1.67 months, 95% CI 24.37-30.94, P=0.130

Progression-free survival of patients according to treatment arms is shown in Figure 3.

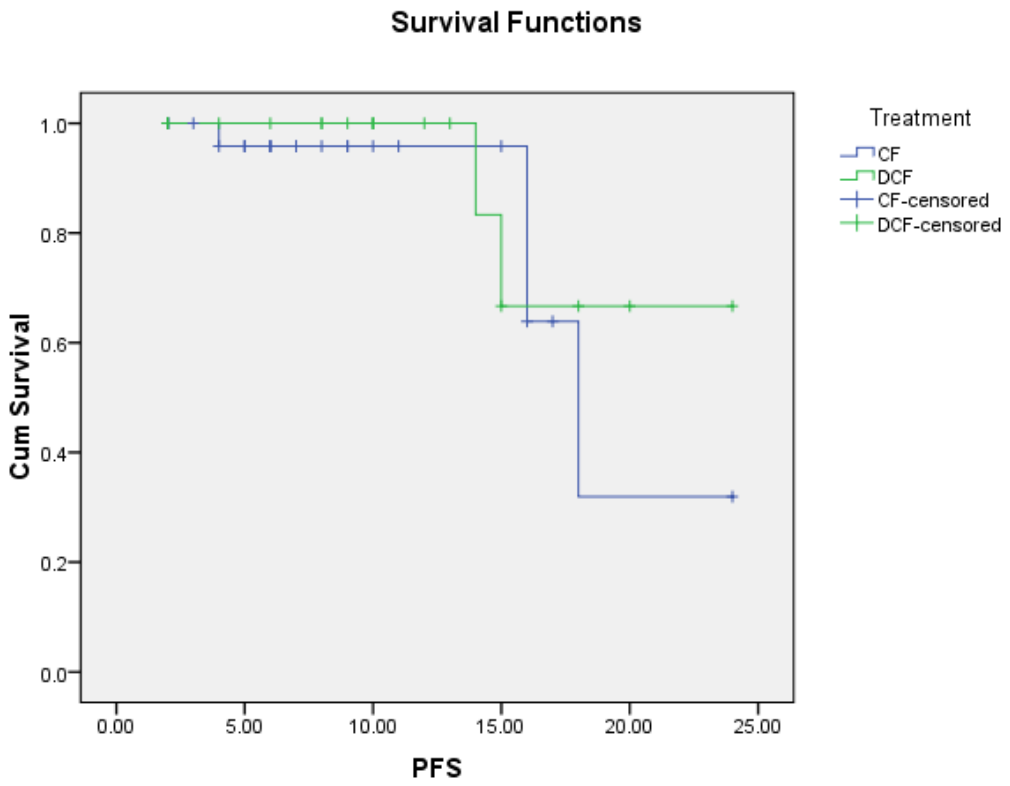

Figure 3: Progression-free survival (PFS) of patients with esophageal cancer treated with chemoradiation, mean PFS of DCF = 20.83±1.83 months, 95% confidence interval (CI) 17.24-24.42, PFS of CF= 18.69±1.75months, 95% CI 15.25-22.23, P=0.229

DISCUSSION

Overall 5-year survival for patients with esophageal cancer is poor. Some improvement has been achieved with the use of concurrent chemoradiation(CRT) over radiotherapy (RT) alone in unresectable cases[11]. The most commonly used agents have been fluorouracil and cisplatin (CF) but with unsatisfactory overall survival benefit [5]. Therefore, more effective regimens have been investigated to improve the prognosis of patients with locally advanced esophageal cancer.Previous studies have reported encouraging results for docetaxel,cisplatinand fluorouracil(DCF) [12, 13].

An overview of the literature concerning the efficacy and toxicity of concurrent CF and radiotherapy (50.4 Gy) for stage II/IIIesophageal cancer shows a complete response (CR) rate of 70.6%, 3-year progression-free survival (PFS) and overall survival (OS) 56.6% and 63.8%

respectively and acute grade 3/4 esophagitis 35% and febrile neutropenia 20% was reported[14].

A previous study done by Kato K *et al* evaluated the efficacy and toxicity of CF and radiotherapy (60 Gy) in patients with stage II/III esophageal cancer between April 2000 and March 2002. Complete response was achieved in 62.2%; median survival was 29 months, with 3-year survival rates of 44.7%. Acute toxicities included Grade 3/4 esophagitis (17%), and infection without neutropenia (12%). Grade 3/4 late toxicities comprised esophagitis (13%), pericardial (16%) and radiation pneumonitis (4%), causing 4 deaths[4].

The results of the present study of CF+ RT for stage II/III esophageal cancer revealed an overall response rate of 35.5%, mean PFS 18 months and OS 27 months. Acute grade 3/4 febrile neutropenia 16% and esophagitis 16% were reported. These results were not in agreement with the previous literatures results. This is may be due to the use of higher or protracted doses of chemotherapy, additional cycles were given to complete responders or due to the inclusion of patients with non-T4/N2 in their studies.

A phaseI/IIstudywas aimed to evaluate the efficacy and safety of docetaxel, cisplatin, and 5-fluorouracil as combinationchemoradiotherapy(DCF-RT) for patients withesophageal cancer. They reported a CR and overall response rate of 54.1 and 83.8 %, respectively. In patients with a clinicalT4, the CR and overall response rate were 47.6 and 85.7 %, respectively. The 2-year OS, 2-year PFS, and median survival time were 52.9, 50.0 %, and 24.7 months, respectively[13].

The present study revealed that patients treated with DCF-RT had an overall response rate of 65%, mean OS and PFS were 20 and 30 months respectively. The most frequent toxicity was leucopoenia66.6% and esophagitis 23.8%. Our results were not comparable with the previous results and this may be due to the higher doses chemotherapy and radiotherapy (60 Gy) and a higher percentage of T4 in their study.

A phase II study was designed to confirm the efficacy and toxicity of DCF-R in advanced esophageal cancer reported an overall response rate of 60 %, median PFS and OS 11, 29 months respectively. They concluded that DCF-R frequently caused myelosuppression and esophagitis but was highly active regimen in advanced esophageal cancer [12].

A comparison of the survival outcomes and toxicity of definitive CRT with either cisplatin/5-fluorouracil (PF) or docetaxel/cisplatin (DP) in patients with unresectableesophageal squamous cell carcinoma was done. The study revealed that the DP group had significantly better OS and PFS. Grade 3-4 esophagitis was more common in the PF group, whereas grade 3-4 thrombopenia and skin toxicities were significantly more common in the DP group than the PF group [14].

In the current study, compared with CF arm, the DCP arm had significantly better OS in subgroup analysis of patients with T3, N+ and stage III. Leucopoenia and febrile neutropenia were significantly higher with DCF-R. These results were in agreement with the results of the study comparing PF vs. DP which revealed that patients with T2/3 and stage III had a better survival with DP+RT[15].

A phase III trial was done to confirm the superiority of DCF versus CF with RT as preoperative therapy for squamous cell carcinoma of esophagus from 41 Japanese institutions within 6.25 years[16].High local control rate and pathological remission rate have been reported with DCF with or without RT for patients who had inoperable esophageal cancer [17].

In this study, we observed that the overall response of the whole cohort was 47%; the mean PFS and OS rates for the study cohort were 19 and 29 months respectively.

A systematic review was done to evaluate the value of concurrent CRT with elective nodal irradiation (ENI) as a standard of care for esophageal cancer reported that the median OS was 21.0 months; 56.8% CR and 85.8% overall response rate[18].

A review of the literature was performed to assess the role of CRT in the treatment ofesophageal cancer. The review reported that preoperative CRT is now used in patients with locally advanced squamous cell carcinoma and definitive CRT without surgery has emerged as a non-surgical approach in the treatment of resectableesophageal carcinoma, whereas salvage surgery is reserved for patients with persistent disease[19].

Several factors can cause survival differences between centers treating locally advanced esophageal cancer by definitive CRT. First, diagnostic imaging of TNM staging and second quality assurance to prevent insufficient irradiation could be prognostic factors affecting survival. Despite of these factors, a study done by Hamamoto Y *et al* did not show inter-institutional heterogeneity[20].

CONCLUSION

Concurrent chemoradiotherapy is an effective non-surgical treatment for stageII/IIIesophageal cancer.Chemoradiotherapy with docetaxel, cisplatin and 5-fluorouracil (DCF) compared with cisplatin and 5-flurouracil improved survival in stage III esophageal cancer patients, but resulted in increase in toxicity.

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