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Combined modality therapy for patients with esophageal squamous cell carcinoma: Radiation dose and survival analyses

Pei-Wei Shueng[1,2] | Chun-Chieh Huang[3] | Yu-Ming Liu[2,4] | Yuan-Hong Wu[2,4,5] | Pin-I Huang[2,4] | Sang-Hue Yen[4,6] | Kuan-Heng Lin[1,5] | Chen-Xiong Hsu[1,4,5]

[1]Division of Radiation Oncology, Department of Radiology, Far Eastern Memorial Hospital, New Taipei City, Taiwan

[2]School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

[3]Division of Medical Imaging, Department of Radiology, Far Eastern Memorial Hospital, New Taipei City, Taiwan

[4]Division of Radiation Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan

[5]Department of Biomedical Imaging and Radiological Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan

[6]Department of Radiation Oncology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

Correspondence
Chen-Xiong Hsu, Division of Radiation Oncology, Department of Radiology, Far Eastern Memorial Hospital, New Taipei City 220, Taiwan.
Email: xc710077@gmail.com

Abstract

Background: We aimed to analyze the radiation dose and compare survival among combined modality therapy using modern radiation techniques for patients with esophageal squamous cell carcinoma (ESCC).

Methods: This retrospective study included patients with clinically staged T1-4N0-3M0 ESCC from 2014 to 2018. Patients who received combined modality therapies with curative intent were enrolled. The overall survival (OS) rates among combined modality therapy were compared. The clinical variables and impacts of radiation dose on survival were analyzed by the Kaplan–Meier method and Cox regression model.

Results: Of the 259 patients, 141 (54.4%) received definitive concurrent chemoradiotherapy (DCCRT); 67 (25.9%) underwent neoadjuvant chemoradiotherapy followed by surgery (NCRT+S); 51 (19.7%) obtained surgery followed by adjuvant chemoradiotherapy (S+ACRT). Two-year OS rates of the DCCRT, NCRT+S and S+ACRT group were 48.9, 61.5 and 51.2%. In the subgroup analysis of DCCRT group, the 2-year OS of patients receiving radiation dose 55–60 Gy was 57.1%. Multivariate analyses showed that clinical stage ($p = 0.004$), DCCRT with 55–60 Gy ($p = 0.043$) and NCRT+S with pathological complete response (pCR) ($p = 0.014$) were significant prognostic factors for better OS. The radiation dose–survival curve demonstrated a highly positive correlation between higher radiation dose and better survival.

Conclusion: Our results suggest that NCRT+S can provide a favorable survival for patients with ESCC, especially in patients who achieved pCR. The optimal radiation dose might be 55–60 Gy for patients receiving DCCRT via modern radiation techniques. Further randomized clinical studies are required to confirm the survival benefits between NCRT+S and DCCRT with escalated dose.

KEYWORDS
concurrent chemoradiotherapy, esophageal cancer, radiation dose, surgery

INTRODUCTION

Combined-modality for esophageal cancer patients provides favorable outcomes as compared to surgery or radiotherapy alone.[1–6] Definitive concurrent chemoradiotherapy (DCCRT) as the primary treatment has been suggested for patients with unresectable disease or medically unfit for surgery.[6,7]

In the setting of DCCRT, the Radiation Therapy Oncology Group (RTOG) 85-01 trial recommended 50 Gy in 25 fractions as the standard radiation dose.[6] Furthermore, the results of Intergroup (INT) 0123 demonstrated that the dose escalation (64.8 vs. 50.4 Gy) did not show survival benefits for patients receiving DCCRT.[7] Since the remarkable studies of RTOG 85-01 and INT 0123 in the conventional

Pei-Wei Shueng and Chun-Chieh Huang contributed equally to this study.

radiotherapy era, modern radiotherapy techniques have greatly advanced which intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), as well as tomotherapy could precisely deliver a higher radiation dose to the tumor while limiting unnecessary doses to the surrounding normal organs.[8–10]

Therefore, in this study, we aimed to analyze the treatment results and compare survival among combined modality therapy via modern radiation techniques for patients with esophageal squamous cell carcinoma (ESCC).

METHODS

Study population

Between January 2014 and December 2018, medical records of patients with histologically confirmed and clinically T1-4N0-3M0, stage II-IVA ESCC in our institution were reviewed. Exclusion criteria were as follows: Patients who had palliative surgical procedure, previous thoracic surgery, previous cancer history, second primary malignancy, corrosive injury of upper GI tract, or poor performance status (Eastern Cooperative Oncology Group ≧ 3) were excluded. The study was approved by the Research Ethics Review Committee of Far Eastern Memorial Hospital (FEMH-IRB no: 108069-E).

Chemoradiotherapy and surgery

Radiotherapy was delivered by modern VMAT or tomotherapy techniques. The initial prescribed dose was 45–50.4 Gy for the gross tumor, lymph node(s), subclinical disease and adjacent lymphatics. For patients with residual disease, a focal boost was given to the gross tumor up to a total dose of 50.4–65 Gy based on each patient's tolerance and at the physician's discretion. Concurrent cisplatin-based chemotherapy for two cycles was scheduled for patients receiving concurrent chemoradiotherapy.

Esophagectomy with curative intent included removal of the primary esophageal tumor with surrounding draining lymph nodes dissection or sampling. Gastric tube reconstruction was then performed and pulled to the cervical incision for anastomosis.

Follow-up of patients

Patients were followed up at clinics of our multimodality treatment team every 3 months for the first 2 years and every 6 months in the subsequent years. Follow-up visits included CT scan of the neck/chest/abdomen, ultrasonography and bone scans as indicated clinically. Esophagoscopy with biopsies were performed for any suspicious recurrent esophageal lesion. Overall survival (OS)

TABLE 1 Patient characteristics

	DCCRT	NCRT+S	S+ACRT	*p*-value
No. of patients	141	67	51	
Age at diagnosis (years)				
Median	62	56	64	0.146
Range	34–89	40–79	35–80	
Gender				
Male	130	64	49	0.383
Female	11	3	2	
Performance status				0.523
ECOG 0–1	102	65	50	
ECOG 2	39	2	1	
Clinical T stage				0.819
T1	0	6	1	
T2	41	16	9	
T3	75	41	29	
T4	25	4	12	
Clinical N stage				0.362
N0	14	9	17	
N1∼3	127	58	34	
Clinical stage				0.155
II	55	28	14	
III	63	36	35	
IVA	23	3	2	
Radiation dose (Gy)				0.015*
Median	56	50.4	50.4	
Range	45–65	45–50.4	45–60	
Location of primary tumor				
Upper third	39	12	4	
Middle third	67	38	32	
Lower third	35	17	15	
Pathological T stage				NA
T0	NA	17	0	
T1	NA	11	0	
T2	NA	16	7	
T3	NA	20	30	
T4	NA	3	14	
Pathological N stage				NA
N0	NA	35	11	
N1∼3	NA	32	40	
Pathological stage				NA
0	NA	17	0	
I	NA	8	0	
II	NA	24	18	
III	NA	13	30	
IVA	NA	5	3	

Abbreviations: DCCRT, definitive concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; NA, not applicable; NCRT+S, neoadjuvant chemoradiotherapy followed by surgery; S+ACRT, radical surgery followed by adjuvant chemoradiotherapy.
*$p < 0.05$.

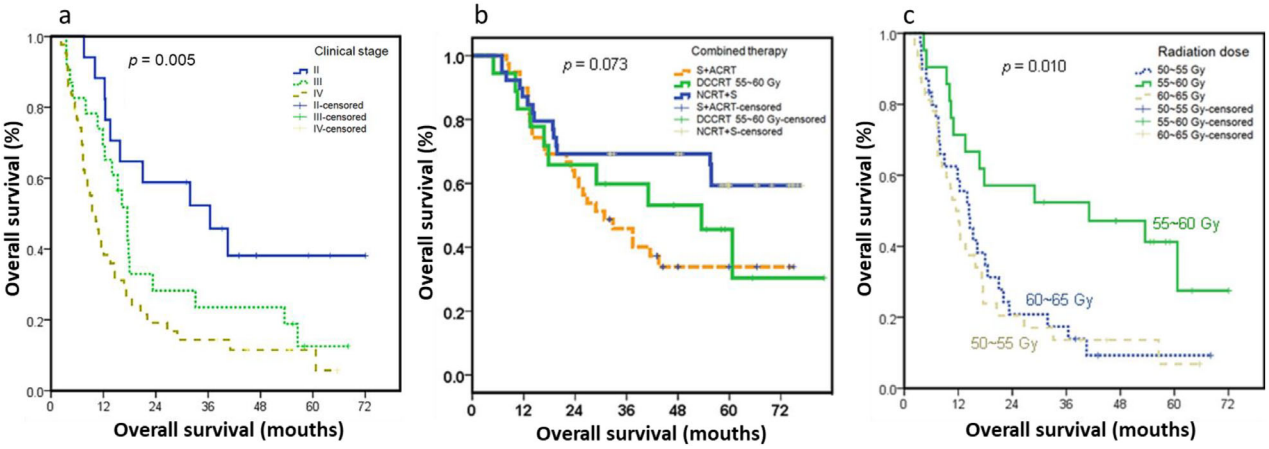

FIGURE 1 Overall survival (Kaplan–Meier method) stratified by (a) clinical stage; (b) combined therapy; (c) radiation dose groups. S+ACRT, surgery followed by adjuvant chemoradiotherapy; DCCRT, definitive concurrent chemoradiotherapy; NCRT+S, neoadjuvant chemoradiotherapy followed by surgery

was calculated from the date of diagnosis to the date of event or last follow-up.

Statistical analysis

The OS rates among patients receiving combined modality therapy were analyzed using the Kaplan–Meier method. Multivariate analyses were performed using the Cox regression method to determine the prognostic factors and impacts of radiation dose on OS. A p-value < 0.05 was considered statistically significant. All statistics were performed with SPSS software version 24.0 (SPSS Inc).

RESULTS

Study population

The patient characteristics are shown in Table 1. Of those enrolled in the study, 259 patients received combined modality therapies with curative intent, 141 (54.4%) received definitive concurrent chemoradiotherapy (DCCRT) as the primary treatment, 67 (25.9%) underwent neoadjuvant chemoradiotherapy followed by surgery (NCRT+S), and 51 (19.7%) obtained surgery followed by adjuvant chemoradiotherapy (S+ACRT). Patients in the NCRT+S group were relatively younger (median age: 56 years) than those in the DCCRT and S+ACRT groups. In the NCRT+S group ($n = 67$), 17 (25.4%) patients achieved a pathological complete response (pCR), and 62 (92.5%) patients achieved R0 complete resection. The distribution of patients in gender, performance status, clinical stage, and location of primary tumor showed no significant differences among different treatment modalities. Patients in the DCCRT group received a higher radiation dose (median dose 56 Gy, range 45–65 Gy) than those in the other groups ($p = 0.015$).

TABLE 2 Multivariable analysis for overall survival (Cox regression)

Variables	Hazard ratio	95% CI	p-value
Age at diagnosis	0.986	0.967–1.005	0.484
Clinical stage II–III (vs. IV)	0.484	0.294–0.798	0.004*
RT dose group			
50–55 Gy	Reference	Reference	0.030*
55–60 Gy	0.458	0.245–0.855	
60–65 Gy	0.860	0.459–1.614	
Location of primary tumor			
Upper third	Reference	Reference	0.480
Middle third	0.677	0.466–1.155	
Lower third	0.865	0.336–1.538	
pCR (vs. non-pCR)	0.512	0.394–0.898	0.014*
R0 resection (vs. R1 + R2)	0.626	0.182–2.110	0.528

Abbreviations: CI, confidence interval; CR, complete response; RT, radiation therapy.
*$p < 0.05$.

Overall survival

The median follow-up time was 22.6 months for all patients (range, 6.3–74.2 months). Survival curves of patients stratified by clinical stage, combined modality and radiation dose group are shown in Figure 1(a)–(c). Two-year OS rates of the DCCRT, NCRT+S and S+ACRT groups were 48.9%, 61.5 and 51.2%, respectively. Two-year OS rates of stage II, III and IV were 58.8, 27.1 and 20.6%, respectively ($p = 0.050$) (Figure 1(a)). Statistically significant differences were found in pretreatment clinical stage ($p = 0.005$), DCCRT with radiation dose 55–60 Gy ($p = 0.010$). In the subgroup analysis of patients receiving DCCRT, the 2-year OS of radiation dose 50–55, 55–60 and 60–65 Gy was 20.8, 57.1 and 20.5%, respectively ($p = 0.010$) (Figure 1(c)).

Multivariate analyses for OS showed that clinical stage II–III ($p = 0.004$), DCCRT with 55–60 Gy ($p = 0.030$), and

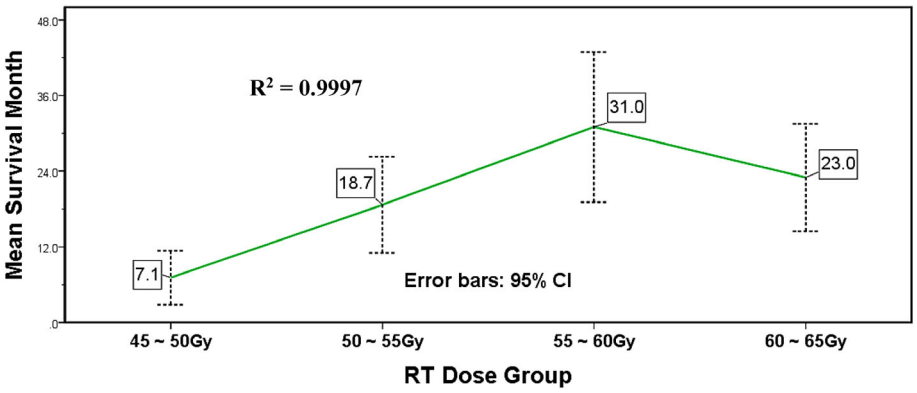

FIGURE 2 Radiation dose–survival curve of the patients receiving DCCRT. Based on the radiation dose, patients were divided into the 45–50, 50–55, 55–60 and 60–65 Gy groups. There was a highly positive correlation ($R^2 = 0.997$) between the higher radiation dose and better survival

TABLE 3 Toxicities grade 3 or more among the dose groups of DCCRT

	45–50 Gy $n = 32$ (%)	50–55 Gy $n = 39$ (%)	55–60 Gy $n = 38$ (%)	60–65 Gy $n = 32$ (%)
Leukopenia	7 (21.9%)	6 (15.4%)	8 (21.1%)	7 (21.9%)
Anemia	5 (15.6%)	5 (12.8%)	6 (15.8%)	4 (12.5%)
Thrombocytopenia	2 (6.25%)	3 (7.69%)	2 (5.26%)	1 (3.13%)
Radiation pneumonitis	1 (3.13%)	0 (0.00%)	1 (2.63%)	1 (3.13%)
Dermatitis	0 (0.00%)	0 (0.00%)	1 (2.63%)	1 (3.13%)
Weight loss	3 (9.38%)	4 (10.3%)	2 (5.26%)	3 (9.38%)
Nausea	3 (9.38%)	3 (7.69)	2 (5.26%)	2 (6.25%)

Note: Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 4.0.

NCRT+S with pCR ($p = 0.014$) were significant prognostic factors for better OS (Table 2).

Radiation dose and survival relationship of patients receiving DCCRT

In patients receiving DCCRT, the mean survival time of the 45–50, 50–55, 55–60 and 60–65 Gy dose groups was 7.1, 18.7, 31.0 and 23.0 months, respectively. The radiation dose–survival curve demonstrated a positive correlation ($R^2 = 0.997$) between the higher radiation dose and better survival in Figure 2. The optimal radiation dose level effect on survival in our study was 55–60 Gy. An additional dose higher than 60 Gy did not further improve survival.

Treatment-related toxicities of patients receiving DCCRT

Treatment-related toxicities grade 3 or more among the dose groups of 141 patients receiving DCCRT are listed in Table 3. The common toxicities grade 3 or more were leukopenia 19.9% (28/141), anemia 14.2% (20/141), and weight loss 8.51% (12/141). There was no significant difference in toxicities grade 3 or more among the dose groups of DCCRT (Fisher's exact test, $p = 0.160$).

DISCUSSION

Combined modality therapies including surgery, chemotherapy and radiotherapy have been applied for improving the survival rates of esophageal cancer patients. Many randomized trials have assessed the survival benefits of NCRT+S; however, the results are variable. The CALGB 9781 trial and the chemoradiotherapy for esophageal cancer followed by surgery study demonstrated a significant survival benefit for the NCRT+S group as compared with esophagectomy alone,[1,11] whereas the FFCD 9901 trial showed that neoadjuvant chemoradiotherapy did not improve OS for esophageal cancer compared with surgery alone.[12] Also, some researchers have indicated that the potential drawbacks of neoadjuvant chemoradiotherapy include increased morbidity, increased toxicity after chemoradiotherapy and a delay in curative surgical management.[13–15]

For esophageal cancer patients who are medically unfit or who have unresectable localized disease, DCCRT is an alternative option. Several randomized controlled studies have demonstrated that DCCRT for ESCC may offer a comparable survival to standard surgery,[4,16] especially in patients who respond to chemoradiation. Although modern radiotherapy techniques using IMRT or VMAT which provide significantly better normal tissue sparing have been widely applied in recent years, the optimal radiation dose for esophageal cancer still remains controversial.[8,10,17–20]

Previous trials using multimodality approaches successfully delivered DCCRT doses >50 Gy without excess morbidity.[4,21] A retrospective study focused on radiation dose escalation for esophageal cancer demonstrated that a higher radiation dose >50 Gy significantly improved locoregional control and overall survival.[17] In an up-to-date meta-analysis of 12 studies including 10 896 esophageal patients receiving DCCRT with modern IMRT or VMAT techniques, the results indicated that high-dose radiotherapy, especially ≥60 Gy, could improve the locoregional control and survival without increase in severe adverse effects as compared with low-dose radiotherapy.[22]

In our study, patients with clinical stage II–IVA ESCC were treated with DCCRT, NCRT+S and S+ACRT using modern VMAT or tomotherapy techniques. We found that NCRT+S provided a better 2-year survival rate of 61.5% as compared with DCCRT (48.9%) and S+ACRT (51.2%). Although patients receiving DCCRT had relatively more advanced T3–T4 disease, the radiation dose delivered to the DCCRT group (median 56 Gy, range 45–65 Gy) was also relatively higher than those of the NCRT+S (median 50.4 Gy, range 45–50.4 Gy) and S+ACRT (median 50.4 Gy, range 45–60 Gy) groups. Notably, subgroup analyses in this study showed that DCCRT with radiation dose 55–60 Gy may have a potential comparable 2-year OS as compared with the NCRT+S group (57.1% vs. 61.5%). However, a radiation dose higher than 60 Gy did not further improve survival for DCCRT patients in the analyses of radiation dose–survival curve. Interestingly, Zhang et al.[17] also found a positive correlation between higher radiation dose and increased locoregional control. Given these observations, there might be a plateau or a threshold of tumor response to radiation dose by the flattened slope in the high-dose area on the dose–response curve. Therefore, the optimal radiation dose in our study might be 55–60 Gy for patients receiving DCCRT via modern radiation techniques.

The limitations of our study included the retrospective nature, heterogeneity in the pretreatment characteristics of patients and lack of detailed locoregional or distant failure patterns among patients receiving DCCRT, NCRT+S and S+ACRT. Moreover, some patients who were initially scheduled to receive neoadjuvant NCRT+S may shift to the DCCRT group, either due to disease progression, medical unfitness for surgery or refusal of further surgery after neoadjuvant chemoradiotherapy. The boost radiation dose to a total dose of 50.4–65 Gy for these crossover patients might be still suboptimal, and the unplanned gaps of total treatment time may also affect the treatment outcomes. Nevertheless, further randomized prospective clinical studies with an intention-to-treat analysis to clarify the survival benefits between NCRT+S and DCCRT with escalated dose are required.

In conclusion, our results suggest that NCRT+S can provide a favorable survival for patients with ESCC, especially in patients who achieved pCR. The optimal radiation dose might be 55–60 Gy for patients receiving DCCRT using modern radiation techniques. Further randomized clinical studies are required to confirm the survival benefits between NCRT+S and DCCRT with escalated dose.

AUTHOR CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization: PW Shueng and YM Liu. Methodology: CX Hsu, PI Huang and YM Liu. Investigation: CX Hsu, YH Wu, PI Huang and SH Yen. Formal Analysis: CX Hsu and CC Huang. Resources: CX Hsu, YH Wu, PI Huang and SH Yen. Writing - Original Draft: PW Shueng and CC Huang. Writing - Review & Editing: Yu-Ming Liu, Pin-I Huang, and CX Hsu. Visualization: CX Hsu and KH Lin. Supervision: CX Hsu. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no competing interests.

ORCID

Chen-Xiong Hsu https://orcid.org/0000-0002-5541-6375

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