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Adjuvant Chemotherapy and Dose Escalation in Definitive Concurrent Chemoradiotherapy for Esophageal Squamous Cell Carcinoma

HYEON KANG KOH[1*], YOUNGHEE PARK[2*], TAERYOOL KOO[3], HAE JIN PARK[4], ME YEON LEE[3], AH RAM CHANG[2], SEMIE HONG[1] and HOONSIK BAE[3]

[1]*Department of Radiation Oncology, Konkuk University School of Medicine and Konkuk University Medical Center, Seoul, Republic of Korea;*
[2]*Department of Radiation Oncology/CyberKnife Center, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea;*
[3]*Department of Radiation Oncology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Gyeonggi-do, Republic of Korea;*
[4]*Department of Radiation Oncology, Hanyang University College of Medicine, Seoul, Republic of Korea*

Abstract. *Background/Aim: To validate the effect of treatment intensification on survival in esophageal squamous cell carcinoma (ESCC) patients undergoing definitive concurrent chemoradiotherapy (dCCRT). Patients and Methods: We reviewed the medical records of 73 ESCC patients who underwent dCCRT between 2006 and 2017 in 3 institutions. Results: The median follow-up time was 13.3 months. The median overall survival (OS) and locoregional recurrence-free survival (LRFS) were 13.3 and 11.2 months, respectively. The median radiotherapy dose was 55.8 Gy, and the median biologically effective dose (BED) was 65.8 Gy. Chemotherapy was given in all patients during dCCRT, and adjuvant chemotherapy was administered in 56 patients (76.7%). Adjuvant chemotherapy improved OS (3-year, 24.2% vs. 11.8%, p=0.004). Higher BED ≥70 Gy improved LRFS (3-year, 41.7% vs. 23.6%, p=0.035). Conclusion: The addition of chemotherapy after dCCRT improves OS. A higher radiotherapy dose improved LRFS, but not OS. Adjuvant chemotherapy should be considered after dCCRT for better outcomes.*

*These Authors contributed equally to this study

Correspondence to: Taeryool Koo, MD, Ph.D., Department of Radiation Oncology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, 22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang-si, Gyeonggi-do, 14068, Republic of Korea. Tel: +82 313803901, Fax: +82 313803913, e-mail: kootaeryool@hallym.or.kr

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Esophageal cancer is the 7th most common cancer worldwide, with more than 500,000 incident cases diagnosed annually (1). The incidence of esophageal cancer significantly varies geographically, with the incidence being the highest in Eastern Asia and Eastern and Southern Africa. The histologic types also markedly differ, with squamous cell carcinoma accounting for 90% of all cases (2). While the prevalence of esophageal squamous cell carcinoma (ESCC) has been decreasing in Western countries, there have been no marked improvements in incidence in Asia and Sub-Saharan Africa (2). In Korea, squamous cell carcinoma is also the predominant type of esophageal cancer, accounting for more than 90% of all cases. Although the age-standardized incidence rates per 100,000 population decreased from 4.1 in 1999 to 2.7 in 2016, survival outcomes remain poor, with a 5-year survival rate of 37.4% (3, 4).

Surgical resection is the mainstay of treatment for esophageal cancer, but the combination with neoadjuvant chemoradiotherapy yields better survival than surgery alone (5). However, less than a third of patients are resectable because of the challenging anatomical location, wide disease extent, and poor performance status on diagnosis. Patients who have unresectable esophageal cancer or are ineligible for surgery are recommended for radiotherapy (RT) as the locoregional treatment modality. Definitive concurrent chemoradiotherapy (dCCRT) has been reported to achieve better survival than RT alone in esophageal carcinoma (6, 7). Several intensified treatment modalities, such as the addition of neoadjuvant chemotherapy or escalation of RT dose, have also been attempted to improve treatment outcomes, but the results were unsatisfactory (8-10).

Currently, the recommended dCCRT regimen for ESCC is an RT dose of 50-50.4 Gy combined with 5-fluorouracil (5-FU) and cisplatin (11, 12). Although modern RT techniques are expected to improve the potential benefit of treatment intensification, there has been no clear evidence on such benefit from randomized controlled trials. This study aimed to validate the effect of treatment intensification on survival in ESCC patients undergoing dCCRT with modern RT techniques.

Patients and Methods

This study was approved by the Institutional Review Board (IRB) of each participating hospital. A waiver of informed consent was approved by each IRB. We retrospectively reviewed the medical records of ESCC patients who underwent dCCRT between 2006 and 2017 in any of the three hospitals. Patients with multiple primary cancers or metastatic disease and those who underwent esophagectomy or RT with palliative aim were excluded. In total, 73 patients were included in this study. The collected data included patient characteristics, clinical and pathological information, and details of treatment for ESCC. The location of the primary tumors was classified according to the distance from the upper incisors: cervical for up to 18 cm, upper thoracic from >18 to 24 cm, middle thoracic from >24 to 32 cm, and lower thoracic from >32 to 40 cm. The length of the primary tumor was measured *via* esophagogastroduodenoscopy.

Given that the length of the primary tumors and the RT dose were continuous variables, they were thus categorized into two groups using Maxstat, the maximally selected rank method in R 3.5.1 (R Development Core Team, Vienna, Austria) (13). Adverse events were categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5. Adverse effects that occurred within 3 months after the completion of dCCRT were categorized as acute, while those that occurred after 4 months of dCCRT were classified as chronic.

Overall survival (OS) was calculated from the date of pathologic diagnosis of ESCC to the date of death or the last follow-up. Meanwhile, the date of disease recurrence or death was used as the end date for progression-free survival (PFS) and locoregional recurrence-free survival (LRFS). The sites of locoregional failure (LRF) and distant metastasis (DM) were recorded for the analysis of failure pattern. The Kaplan–Meier method was used to estimate the survival rates and plot survival curves. For univariate and multivariate analyses, we used the log-rank test and Cox proportional-hazards model, respectively. Pearson's Chi square test or the linear-by-linear association test was used to verify differences in categorical variables. Variables with a p-value of <0.05 in the univariate analyses were included in the multivariate analyses. We used Predictive Analytics Software, version 18.0 (SAP America, Inc., Newtown Square, PA, USA) for statistical analyses.

Results

Patients. The median patient age was 66 years (range=47-84 years), and the majority was men (94.5%). With respect to the primary tumor location, 5 patients (6.8%) had cervical, 13 patients (17.8%) had upper thoracic, 36 patients (49.3%) had middle thoracic, and 19 patients (26.0%) had lower thoracic ESCCs. The median length of primary tumors was 5 cm (range=1.5-14 cm). The patient and tumor characteristics are detailed in Table I.

Treatments. The median total RT dose was 55.8 Gy (range=50-70 Gy), and the median daily dose was 1.8 Gy (range=1.8-2 Gy). When we calculated the biologically effective dose (BED) with $\alpha/\beta=10$, the median BED was 65.8 Gy (range=59.5-84 Gy). Three-dimensional conformal RT (3D-CRT) was used in 63 patients (86.3%), and intensity-modulated RT (IMRT) was used in 10 patients (13.7%). The majority of the patients (68 patients, 93.2%) received a combination of 5-FU and cisplatin, while 5-FU (n=3) or cisplatin (n=1) alone was given for the remaining patients. Induction chemotherapy was administered in 4 patients using 5-FU and cisplatin. Adjuvant chemotherapy comprising 5-FU and cisplatin was administered in 56 patients (76.7%).

Treatment outcomes and prognostic factors. The median follow-up time was 13.3 (95% confidence interval=15.7-25.8) months. The median OS, PFS, and LRFS were 13.3, 8.1, and 11.2 months, respectively. The OS, PFS, and LRFS rates were 21.2%, 16.3%, and 32.7% at the 3 year follow-up, respectively (Figure 1). Patients receiving adjuvant chemotherapy had better OS (3 years, 24.2% *vs*. 11.8%, $p=0.004$) and PFS (3 years, 19.6% *vs*. 5.9%, $p=0.004$) than those not receiving adjuvant chemotherapy. Patients with higher RT dose of BED ≥70 Gy showed better LRFS (3 years, 41.7% *vs*. 23.6%, $p=0.035$) than those with BED <70 Gy.

Univariate analysis to evaluate prognostic factors showed that age, T stage, N stage, and primary tumor length were significantly associated with OS. Meanwhile, T stage, N stage, and primary tumor length were independent factors of PFS. For LRFS, T stage, N stage, and primary tumor length were related with better outcomes.

In multivariate analysis, T stage and N stage remained as the prognostic factors of OS, PFS, and LRFS. Age was correlated with OS only. Regarding treatment factors, the addition of adjuvant chemotherapy was associated with better OS and PFS. BED ≥70 Gy was associated with better LRFS. The results of multivariate analyses are summarized in Table II. Survival curves according to the treatment factors are presented in Figure 2.

Initial failure patterns and salvage treatments. LRF was the main pattern of initial failure; 23 patients (53.5%) had LRF, 12 (27.9%) had DM, and 8 (18.6%) had both LRF and DM (Figure 3). The most common sites of DM were the lung (n=17), liver (n=6), bones (n=4), brain (n=2), and others (n=2). Docetaxel-based salvage chemotherapy was administered in 24 patients. Palliative RT was given in 3 patients with mediastinal nodal recurrence, brain metastasis, and liver metastasis.

Table I. *Details of patient and tumor characteristics and univariate analyses.*

Variables		N	(%)	3Y-OS (%)	*p*-Value	3Y-PFS (%)	*p*-Value	3Y-LRFS (%)	*p*-Value
Gender	Male	69	(94.5)	22.5	0.607	17.2	0.533	35.5	0.170
	Female	4	(5.5)	0.0		0.0		0.0	
Age (years)	≤65	33	(45.2)	24.2	0.044	23.1	0.132	35.9	0.576
	>65	40	(54.8)	20.0		10.5		28.7	
Differentiation[1]	Well	8	(11.0)	50.0	0.224	33.3	0.170	58.3	0.634
	Others	45	(61.6)	15.0		14.1		28.6	
Location	Upper[2]	18	(24.7)	20.8	0.567	14.8	0.564	32.0	0.946
	Middle	36	(49.3)	16.2		7.9		30.6	
	Lower	19	(26.0)	31.6		31.6		35.7	
T	T1-2	18	(24.7)	55.6	0.005	47.6	0.001	62.9	0.007
	T3-4	55	(75.3)	11.0		7.3		21.7	
N	N0-1	39	(53.4)	36.3	0.001	25.3	0.003	45.5	0.026
	N2-3	34	(46.6)	5.9		5.9		13.9	
Length	≤2 cm	8	(11.0)	87.5	0.002	56.3	0.002	85.7	0.023
	>2 cm	65	(89.0)	13.4		11.2		24.1	
Induction CTx	No	69	(94.5)	21.2	0.816	17.4	0.865	34.4	0.950
	Yes	4	(5.5)	0.0		0.0		0.0	
Adjuvant CTx	No	17	(23.3)	11.8	0.004	5.9	0.004	21.4	0.201
	Yes	56	(76.7)	24.2		19.6		34.2	
BED (Gy)	<70	40	(54.8)	13.7	0.288	12.0.	0.056	23.6	0.035
	≥70	33	(45.2)	30.1		20.7		41.7	

Y: Year; OS: overall survival; PFS: progression-free survival; LRFS: locoregional recurrence-free survival; CTx: chemotherapy; BED: biologically effective dose. [1]Missing data included. [2]Cervical 5 patients (6.8%) and upper thoracic 13 patients (17.8%) were included.

Adverse effect. The adverse effects are summarized in Table III. A total of 57 acute adverse events and 38 chronic adverse effects were recorded. Acute and chronic grade ≥3 events were noted in 21 (29%) and 19 (26%) patients, respectively. In 56 patients who received adjuvant chemotherapy, 16 (29%) and 17 (30%) had acute and chronic grade ≥3 events, respectively. In 33 patients who received BED ≥70 Gy, 5 (15%) and 5 (15%) experienced acute and chronic grade ≥3 events, respectively.

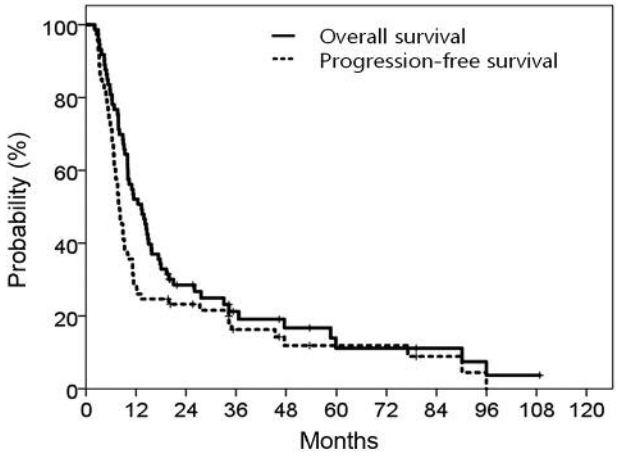

Figure 1. *Survival curves of the entire patient cohort.*

Discussion

ESCC patients have poor prognosis unless they undergo esophagectomy. However, only a small number of patients are eligible for resection. For patients who are ineligible for surgery, dCCRT is recommended. Although dCCRT comprising a total dose of 50-50.4 Gy and cisplatin/5-FU is recommended, various treatment intensification strategies have been investigated to improve outcomes. In the present study, we confirmed the benefit of adjuvant chemotherapy and RT dose escalation in dCCRT for ESCC patients.

The INT 0123 (Radiation Therapy Oncology Group 94-05) study (9) which is the representative trial investigating the benefit of dose escalation, found no significant difference in survival between high-dose (64.8 Gy) and standard-dose (50.4 Gy) RT. A notable finding in the INT0123 was toxicity, with more treatment-related deaths in the high-dose arm (11 *vs*. 2). Also, treatment time was significantly prolonged in the high-dose arm due to treatment breaks. It is well known that treatment breaks or prolonged overall treatment time during RT have detrimental effects on the outcomes (14).

An important cause of these results was the RT technique used during the INT0123 study, which was a conventional multifield RT consisting of anterior/posterior, oblique, or

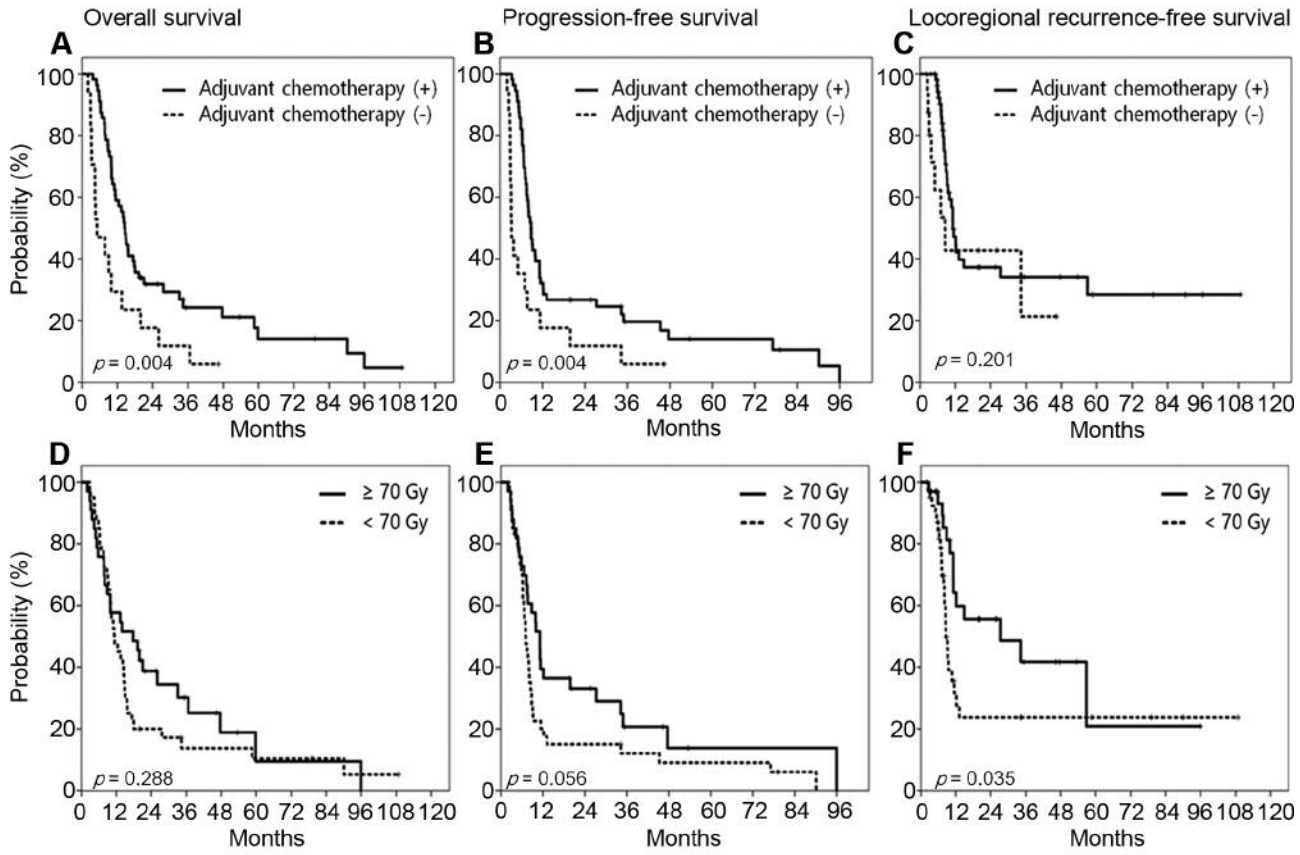

Figure 2. *Kaplan–Meier curves for overall survival (A), progression-free survival (B), and locoregional recurrence-free survival (C) between patients receiving adjuvant chemotherapy and patients not receiving adjuvant chemotherapy. Kaplan–Meier curves for overall survival (D), progression-free survival (E), and locoregional recurrence-free survival (F) between patients with an RT dose of BED ≥70 Gy and patients with BED <70 Gy.*

Table II. *Multivariate analyses*.

Variables	OS		PFS		LRRFS	
	p-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)
Age >65 years	0.011	2.056 (1.179-3.585)	NS		NS	
T3-T4	0.049	2.060 (1.003-4.232)	0.007	2.754 (1.317-5.759)	0.056	2.589 (0.975-6.870)
N2-N3	0.005	2.233 (1.269-3.929)	0.007	2.090 (1.228-3.557)	0.047	2.002 (1.010-3.969)
Length >2 cm	0.055	3.317 (0.974-11.294)	NS		NS	
Adjuvant CTx	0.006	0.429 (0.234-0.788)	<0.001	0.268 (0.141-0.509)	0.020[1]	0.360 (0.151-0.854)
BED ≥70 Gy	NS		0.0211	0.512 (0.291-0.902)	0.024	0.425 (0.202-0.893)

OS: Overall survival; PFS: progression-free survival; LRFS: locoregional recurrence-free survival; HR: hazard ratio; CI: confidence interval; CTx: chemotherapy; BED: biologically effective dose. [1]No significant difference in the univariate analyses.

lateral beams (9). The conformal level of this RT plan was lower than that of recent RT techniques, such as 3D-CRT and IMRT. Consequently, the elevated dose might have affected surrounding critical organs, such as the lung, heart, or spinal cord, as well as the target volume including that for primary tumors and regional lymph nodes (15). Normal-tissue toxicity can be reduced by using 3D-CRT with multiple beam angles. Furthermore, IMRT can allow for dose

Table III. *Adverse effects according to the treatment factors.*

	Acute			Chronic		
	Total (N=73)	Adjuvant CTx (N=56)	BED ≥70 Gy (N=33)	Total (N=73)	Adjuvant CTx (N=56)	BED ≥70 Gy (N=33)
Grade 1	6	5	6	4	4	3
Grade 2	30	24	11	15	10	7
Grade 3	18	14	5	16	14	5
Grade 4	2	2	0	1	1	0
Grade 5	1	0	0	2	2	0

CTx: Chemotherapy; BED: biologically effective dose.

increases of up to 130%-140% more than conventional RT under normal-tissue constraints (16). Although there have been no randomized control studies using 3D-CRT or IMRT, several retrospective studies reported the positive correlation between RT dose and locoregional control (17, 18).

In this study, the escalated dose positively affected locoregional control. The 3-year LRFS rates were 41.7% and 23.6% for patients receiving BED ≥70 Gy and <70 Gy, respectively. Interestingly, grade ≥3 adverse effects were lower in the BED ≥70 Gy group than that in the <70 Gy group (acute adverse effects 15% *vs*. 40%, chronic adverse effects 15% *vs*. 35). Considering the retrospective nature of this study, it would be reasonable to interpret that the severity of adverse effects was not related to the RT dose escalation.

However, there was no difference in OS rates between the BED ≥70 Gy and the <70 Gy groups in our study. Currently, the association between OS and RT dose is unclear even in retrospective studies. While some studies reported positive correlation (19-21), others also reported a negative association (22, 23). Prospective clinical trials using modern RT techniques are needed to evaluate the effect of RT dose escalation on OS.

Another strategy to improve the outcomes of dCCRT for ESCC is the intensification of chemotherapy regimens. The PRODIGE5/ACCORD17 trial (24) aimed to show the benefit of the 5-FU, leucovorin, and oxaliplatin (FOLFOX) regimen *versus* 5-FU and cisplatin. The RT dose was 50 Gy in 25 fractions. However, after a median follow-up time of 25.3 months, there were no significant differences in PFS (median 9.7 *vs*. 9.4 months, p=0.64) and OS (median 20.2 *vs*. 17.5 months, p=0.70) between the FOLFOX and the 5-FU/cisplatin arms. There were also no differences in the rate of grade ≥3 severe adverse effects between the two arms. The RTOG 0113 (10) was a phase II study comparing induction chemotherapy comprising 5-FU, cisplatin, and paclitaxel (arm A) and paclitaxel and cisplatin (arm B). The RT dose was 50.4 Gy in 28 fractions, and the concurrent chemotherapy regimen was 5-FU and paclitaxel. Both arms did not meet the 1-year survival endpoint and reported high morbidity.

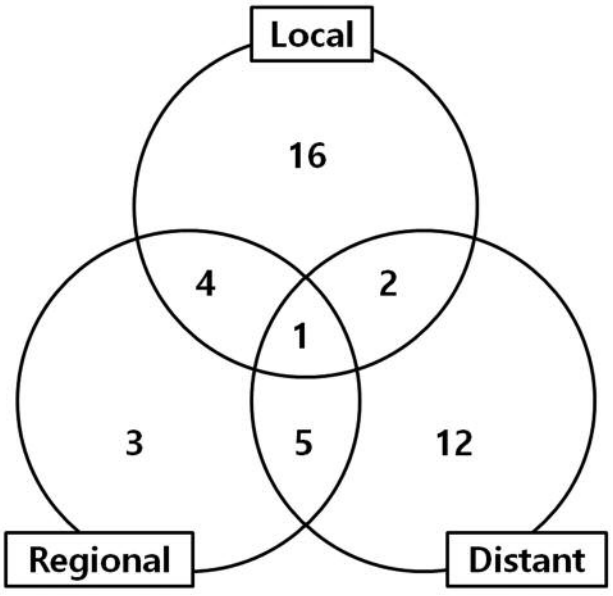

Figure 3. *Initial patterns of failure.*

The addition of targeted agents has also been assessed. The SCOPE1 trial (25) investigated the benefit of adding cetuximab to dCCRT 50 Gy in 25 fractions with cisplatin and capecitabine. However, there were no positive results; the dCCRT plus cetuximab group had worse OS (median 22.1 *vs*. 25.4 months, p=0.004) and more grade 3-4 toxicities (79% *vs*. 63%, p=0.004). The RTOG 0436 trial (26) compared dCCRT alone (RT 50.4 Gy in 28 fractions with cisplatin and paclitaxel) and dCCRT with cetuximab. However, there was also no significant difference in the 2-year OS rates between the dCCRT alone arm and the dCCRT with cetuximab arm within a median follow-up time of 18.6 months (44% *vs*. 45%, p=0.47).

Interestingly, the use of adjuvant chemotherapy after the completion of dCCRT was associated with better OS in our study. There was no significant difference in patient/tumor

characteristics between two groups (data not shown), but the 3-year OS rates were 24.2% in patients who received adjuvant chemotherapy, while it was only 11.8% in those who did not receive adjuvant chemotherapy (p=0.004). With respect to grade ≥3 adverse effects, there was no significant difference in the frequency of acute (29% *vs*. 29%) and chronic (30% *vs*. 26%) toxicities between patients who received adjuvant chemotherapy and the overall patient population (Table III).

Currently, there is no prospective trial investigating the benefit of the addition of adjuvant chemotherapy to dCCRT. Several retrospective studies on dCCRT reported that adjuvant chemotherapy improved OS (21, 27, 28). Wu *et al*. (27) analyzed the outcomes of 209 patients with ESCC who did not undergo surgery. The chemotherapy regimen comprised 5-FU and cisplatin and was similar during or after RT. The median OS was 53.4 months for patients who received adjuvant chemotherapy and 27.0 months for those who did not (p=0.04). Kim *et al*. (28) reviewed the results of 63 locally advanced ESCC patients who received platinum-based chemotherapy combined with 5-FU or docetaxel. Adjuvant chemotherapy improved OS (median, 30.4 *vs*. 12.0 months, p=0.002) in the good risk group.

However, results on the benefit of adjuvant chemotherapy are conflicting. Chen *et al*. (29) evaluated 187 ESCC patients who underwent dCCRT with or without adjuvant chemotherapy and found no significant differences in OS between patients with and without adjuvant chemotherapy (at 2 years, 47.1% *vs*. 39.1%, p=0.732). There was also no significant difference in OS in subgroup analyses according to stage and response. Therefore, the benefit of the addition of chemotherapy to dCCRT should be investigated in clinical trials.

There were several limitations in our study. First, heterogeneous chemotherapy regimens were used in the participating institutions. The influence of chemotherapy dose or cycles on outcomes was not analyzed. Next, detailed RT parameters were hard to collect. The parameters could have been helpful to evaluate the correlation between RT technique and treatment outcomes, for example, whether IMRT can reduce RT-related toxicities or which RT parameters are associated with toxicity or survival. Also, treatment response was not assessed owing to the difficulties in collecting and reviewing the results of imaging studies. The benefit of adjuvant chemotherapy on OS needs to be validated in prospective trials.

Conclusion

The addition of chemotherapy after the completion of dCCRT improved OS in ESCC, but it did not cause additional adverse effects. The incidence of grade ≥3 adverse effects was similar between the patients with adjuvant chemotherapy and the overall patient population. Higher RT dose of BED ≥70 Gy was associated with improved LRFS, but not with OS. It could be a rational strategy to consider adjuvant chemotherapy after dCCRT.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

TK conceptualized and designed this study. HKK, YP, and TK collected and analyzed data. HJP, MYL, ARC, SH, and HB participated in the interpretation of results. HKK and YP drafted the article, and TK revised the article. All Authors read and approved the article.

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