Value and Application of Trimodality Therapy or Definitive Concurrent Chemoradiotherapy in Thoracic Esophageal Squamous Cell Carcinoma

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BACKGROUND: Few large, prospective, randomized studies have investigated the value and optimal application of neoadjuvant chemoradiotherapy followed by surgery (trimodality therapy) or definitive concurrent chemoradiotherapy (CCRT) for patients with thoracic esophageal squamous cell carcinoma (TESCC). METHODS: The authors analyzed data from patients with TESCC in the Taiwan Cancer Registry database. To compare their outcomes, patients with TESCC were enrolled and categorized into the following groups according to treatment modality: group 1, those who underwent surgery alone; group 2, those who received trimodality therapy; and group 3, those who received definitive CCRT. Group 1 was used as the control arm for investigating the risk of mortality after treatment. RESULTS: In total, 3522 patients who had TESCC without distant metastasis were enrolled. Multivariate Cox regression analysis indicated that a Charlson comorbidity index score ≥3, American Joint Committee on Cancer stage ≥IIA, earlier year of diagnosis, alcohol consumption, cigarette smoking, and definitive CCRT were significant, independent predictors of a poor prognosis. After adjustment for confounders, adjusted hazard ratios and 95% confidence intervals (CIs) for overall mortality in patients with clinical stage I, II, III, and IIC TESCC were 2.01 (95% CI, 0.44-6.18), 1.65 (95% CI, 0.99-2.70), 1.48 (95% CI, 0.91-2.42), 0.66 (95% CI, 1.08-114), 0.39 (95% CI, 0.26-0.57), and 0.44 (95% CI, 0.24-0.83), respectively, in group 2; and 2.06 (95% CI, 1.18-3.59), 2.65 (95% CI, 1.76-4.00), 2.25 (95% CI, 1.49-3.59), 1.34 (95% CI, 0.79-2.28), 0.82 (95% CI, 0.57-1.71), and 0.93 (95% CI, 0.51-1.71), respectively, in group 3. CONCLUSIONS: Trimodality therapy might be beneficial for the survival of patients with advanced-stage (IIIA-IIIC) TESCC, and CCRT might be an alternative to surgery alone in these patients. Cancer 2017;123:3904-15. © 2017 American Cancer Society.

KEYWORDS: concurrent chemoradiotherapy (CCRT), squamous cell carcinoma, surgery alone, thoracic esophageal cancer, trimodality therapy.

INTRODUCTION
Squamous cell carcinomas (SCCs) constitute greater than 90% of esophageal cancers in Taiwan.1 The treatments for esophageal cancer also vary, depending on their location, such as in the cervical or thoracic portion of the esophagus or at the gastroesophageal (GE) junction, according to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology and findings from previous studies.2-6 The National Comprehensive Cancer Network guidelines describe various treatments for thoracic esophageal SCC (TESCC).2 Surgery, definitive concurrent chemoradiotherapy (CCRT), and neoadjuvant CCRT followed by surgery (trimodality therapy) are the main therapies for TESCC.2 Surgery has been the standard treatment for TESCC, but surgery as a monotherapy has been challenged.7,8 Data from a contemporary surgical series reveal 5-year survival rates of 15% to 20% for surgery alone.9,10 This poor long-term outcome prompted the evaluation of trimodality therapy and definitive CCRT, with the objective of improving the survival of patients with apparently localized disease.

Of 5 completed randomized trials that have compared trimodality therapy with surgery alone, only 1 reported a statistically significant survival benefit for trimodality therapy after peer review12; 1 was not a peer-reviewed full article; and the remaining 3 trials, 2 of which were underpowered, did not report any survival benefit.13-15 CCRT has now become the standard treatment for TESCC, but surgery as a monotherapy has been challenged.7,8

DOI: 10.1002/cncr.30823, Received: March 3, 2017; Revised: April 12, 2017; Accepted: May 8, 2017, Published online June 13, 2017 in Wiley Online Library (wileyonlinelibrary.com)
the standard nonsurgical treatment option for patients who can tolerate chemotherapy (CT).16 However, only a few studies have compared definitive CCRT with surgery alone for TESCC; most of such studies are prospective phase 1 and 2 clinical trials and small retrospective studies, and a few are small randomized clinical trials and are not specific to TESCC.17-20 The conclusions of these studies could not support the finding that long-term survival after definitive CCRT for TESCC is at least comparable to that after surgery alone. In addition, heterogeneous radiation doses, regimens of CT, different locations of esophageal cancers, various American Joint Committee on Cancer (AJCC) clinical stages, and combined SCCs and adenocarcinomas were present in previous trials or studies.12-14,21-24

To date, few large, prospective, randomized studies have investigated the value and optimal application of trimodality therapy or definitive CCRT in patients with TESCC. The effects of trimodality therapy or CCRT in TESCC require further investigation using modern clinical staging to determine the most appropriate therapy. In the current study, we evaluated the therapeutic effects of trimodality therapy, definitive CCRT, and surgery alone in patients with TESCC by using modern clinical staging, suitable radiotherapy (RT) doses, and similar CT regimens.

MATERIALS AND METHODS
The cohort for this study was established using data from the Taiwan Cancer Registry database. We enrolled patients who received a diagnosis of TESCC between January 1, 2006, and December 31, 2014. The index date was the date of surgery in the surgery and trimodality groups and the date on which treatment was started in the definitive CCRT group. The follow-up duration was from the index date to December 31, 2014. The cancer registry database of the Collaboration Center of Health Information Application contains detailed cancer-related information, including the clinical stage, treatment modalities, pathology, radiation doses, and regimens used (CCRT or neoadjuvant CCRT).1,25-29 Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB no. 201402018). The diagnoses of enrolled patients were confirmed according to their pathologic data, and it was confirmed that patients who received a new diagnosis of TESCC had no other cancer or distant metastasis. The inclusion criteria were a TESCC diagnosis, age ≥20 years, and AJCC clinical cancer stages IA through IIIC (without metastasis). Exclusion criteria were a history of cancer before TESCC diagnosis, distant metastasis, unknown esophageal locations, missing sex data, age <20 years, unclear staging, and non-SCC histology. TESCC was defined as esophageal SCC (ESCC) with pathologic confirmation in the thoracic area recorded in the cancer registry database. In addition, we excluded patients with TESCC who did not receive any treatments, did not receive sufficient RT doses (≥4500 centigray [cGy]) in the trimodality or CCRT groups after TESCC diagnosis, did not receive cisplatin-based CT regimens, received sequential CT and RT, received CT alone, received RT alone, received adjuvant therapy after surgery or adjuvant CCRT, or underwent surgery >12 weeks after CCRT. Finally, we enrolled patients with TESCC and categorized them into the following groups on the basis of treatment modality to compare their outcomes: group 1, those who underwent surgery alone; group 2, those who received neoadjuvant CCRT followed by surgery (trimodality); and group 3, those who received definitive CCRT. The median total RT dose and fraction size was 5040 cGy in 180-cGy fractions for groups 2 and 3, respectively. Comorbidities were scored using the Charlson comorbidity index (CCI).26,30 Only comorbidities observed 6 months before and after the index date were included; comorbid conditions were identified and included according to the main International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for the first admission or more than 2 repeated main diagnosis codes for visits to the outpatient department. Significant independent predictors, such as age, sex, CCI score, AJCC clinical stage, year of diagnosis, RT dose, alcohol consumption, and cigarette smoking, were determined using multivariate Cox regression analysis to determine the hazard ratio (HR); the independent predictors were controlled for adjustment or were stratified in the analysis, and the endpoint was the mortality rate among treatments, with group 1 as the control arm.

The cumulative incidence of death was estimated using the Kaplan-Meier method, and differences among treatment modalities were determined using the log-rank test. After adjustment for confounders, the Cox proportional-hazards method was used to model the time from the index date to all-cause mortality among patients receiving treatment. In the multivariate analysis, HRs were adjusted for age, sex, CCI score, clinical AJCC stage, year of diagnosis, RT modality, RT dose, alcohol consumption, and cigarette smoking. Stratified analyses were performed to evaluate the mortality risk associated with different treatment modalities and different AJCC clinical stages. All analyses were performed using SAS software.
RESULTS

We enrolled 3522 patients who had TESCC without distant metastasis (Table 1). Of these patients, 462 underwent surgery alone (group 1), 903 received neoadjuvant CCRT followed by surgery (group 2; trimodality), and 2157 received definitive CCRT (group 3). The mean ± standard deviation follow-up duration after the index date was 2.73 ± 1.44 years. Older patients (median age, 58.96 years) underwent definitive surgery alone, whereas younger patients received trimodality therapy or definitive CCRT (median age, 54.22 or 56.68 years, respectively) (Table 1). Moreover, 17.75% of patients who had CCI scores ≥3 underwent surgery alone; however, 8.75% of patients who had CCI scores ≥3 received trimodality therapy, and 14.09% received definitive CCRT. Among patients who had AJCC clinical stage IIIC disease, the proportion of those who received definitive CCRT (32.22%) was greater than the proportions of patients who underwent surgery alone (3.03%) and received trimodality therapy (19.16%). Furthermore, the proportion of patients who underwent surgery alone in the earlier years of diagnosis was greater than the proportions of those who received neoadjuvant CCRT followed by

| Characteristic                   | All Patients, N = 3522 | Surgery Alone, n = 462 | CCRT—Surgery, n = 903 | CCRT, n = 2157 | P       |
|---------------------------------|------------------------|------------------------|-----------------------|----------------|---------|
| Age: Median, IQR [min, max], y  | 56.09, 14.41 [23.88, 101.87] | 58.96, 17.69 [37.22, 101.87] | 54.22, 12.20 [23.88, 78.42] | 56.68, 5.02 [29.95, 92.75] | < .0001 |
| Sex                             | Men 3322 (94.32)       | 412 (89.18)            | 857 (94.91)           | 2053 (95.18)   |         |
|                                 | Women 200 (5.68)       | 50 (10.82)             | 46 (5.09)             | 104 (4.82)     |         |
| Follow-up: Mean ± SD, y         | 2.73 ± 1.44            | 3.43 ± 1.85            | 3.08 ± 1.41           | 2.44 ± 1.26    | < .0001 |
| CCI score                       | Mean ± SD              | 1.24 ± 1.35            | 1.60 ± 1.53           | 1.03 ± 1.10    | < .0001 |
|                                 | Median, IQR [min, max] | 1, 2 [0, 9]            | 1, 1 [0, 8]           | 1, 2 [0, 6]    | < .0001 |
|                                 | 0                      | 1183 (33.59)           | 107 (23.16)           | 342 (73.47)    |         |
|                                 | 1                      | 1235 (35.07)           | 156 (33.77)           | 322 (73.47)    | < .0001 |
|                                 | 2                      | 639 (18.14)            | 117 (25.32)           | 160 (35.72)    | < .0001 |
|                                 | ≥3                     | 465 (13.20)            | 82 (17.75)            | 79 (17.85)     | < .0001 |
| AJCC clinical stage             | IA                     | 45 (1.28)              | 36 (7.79)             | 0 (0)          |        |
|                                 | IB                     | 195 (5.54)             | 154 (33.33)           | 6 (0.66)       |        |
|                                 | IIa                    | 294 (8.35)             | 90 (19.48)            | 68 (7.53)      |        |
|                                 | IIb                    | 365 (10.36)            | 100 (21.65)           | 83 (9.19)      |        |
|                                 | IIIC                   | 714 (20.27)            | 28 (6.06)             | 272 (30.62)    |        |
|                                 | IIIb                   | 1027 (29.16)           | 40 (8.66)             | 301 (33.33)    |        |
|                                 | IIIIC                  | 862 (23.04)            | 14 (3.03)             | 173 (19.16)    |        |
| RT dose, cGy                    | ≥6000                  | 735 (24.02)            | 0 (0)                 | 59 (5.33)      | < .0001 |
|                                 | <6000                  | 2352 (75.98)           | 0 (0)                 | 844 (93.47)    | < .0001 |
| RT modality                     | IMRT                   | 2405 (78.59)           | 0 (0)                 | 714 (79.07)    | < .0001 |
|                                 | Non-IMRT               | 655 (21.41)            | 0 (0)                 | 189 (20.93)    | < .0001 |
| Alcohol consumption             | Yes                    | 3077 (87.22)           | 400 (86.58)           | 785 (86.93)    | < .0001 |
|                                 | No                     | 445 (13.00)            | 62 (13.42)            | 118 (13.07)    | < .0001 |
| Cigarette smoking               | Yes                    | 3062 (87.51)           | 399 (86.36)           | 784 (86.82)    | < .0001 |
|                                 | No                     | 440 (12.49)            | 63 (13.64)            | 119 (13.18)    | < .0001 |
| Year of diagnosis               | 2006-2010              | 1337 (37.96)           | 200 (43.29)           | 294 (32.56)    | < .0001 |
|                                 | 2011-2014              | 2185 (62.04)           | 262 (56.71)           | 609 (67.44)    | < .0001 |
| Death                           | Yes                    | 2346 (66.61)           | 165 (35.71)           | 495 (54.82)    | < .0001 |
|                                 | No                     | 1176 (33.39)           | 297 (64.29)           | 408 (45.18)    | < .0001 |

Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson comorbidity index; CCRT, concurrent chemoradiotherapy; cGy, centigrays; CT, chemotherapy; IMRT, intensity-modulated radiotherapy; IQR, interquartile range; max, maximum; min, minimum; RT, radiotherapy; SD, standard deviation.
surgery and those who received definitive CCRT (43.29%, 32.56%, and 39.08%, respectively, in 2006-2010). In groups 1, 2, and 3, the proportions of alcohol consumers were 86.58%, 86.93%, and 87.71%, respectively; and the proportions of cigarette smokers were 86.36%, 86.82%, and 88.04%, respectively (Table 1).

Multivariate Cox regression analysis indicated that CCI scores ≥3, AJCC stage ≥IIA disease, earlier year of diagnosis, alcohol consumption, cigarette smoking, and definitive CCRT were significant, independent predictors of a poor outcome (Table 2). Trimodality therapy (adjusted HR [aHR], 0.87; 95% confidence interval [CI], 0.71-1.06) was not a significant, independent, protective prognostic factor for overall survival (OS) (% = .1631) (Table 2). Definitive CCRT (aHR, 1.73; 95% CI, 1.44-2.08) was a significant, independent poor prognostic factor for OS (% < .0001) (Table 2).

The AJCC clinical stage was identified as a crucial independent predictor. Furthermore, the aHRs increased with advancing stages from stages IIA through IIIC (aHR:

### TABLE 2. Cox Regression Analysis of the Risk of Death Among Patients With Thoracic Esophageal Squamous Cell Carcinoma

| Variable                      | Univariate Analysis | Multivariate Analysis |
|-------------------------------|---------------------|-----------------------|
|                               | HR (95% CI)         | P         | aHR (95% CI) | P         |
| Treatment                     | XML                  | XML                  | XML                  | XML                  |
| Surgery alone, Ref            | 1.00                | XML                  | 1.00                | XML                  |
| CCRT – surgery                | 1.60 (1.34-1.91)    | <.0001              | 0.87 (0.71-1.06)    | .1631              |
| CCRT                          | 3.27 (2.79-3.84)    | <.0001              | 1.73 (1.44-2.08)    | <.0001              |
| Sex                           | XML                  | XML                  | 1.00                | XML                  |
| Women, Ref                    | 1.00                | XML                  | 1.00                | XML                  |
| 1.25 (1.04-1.50)              | .0171               | XML                  | 1.07 (0.89-1.29)    | .4518              |
| Age, y                        | XML                  | XML                  | 1.00                | XML                  |
| 20-29, Ref                    | 1.00                | XML                  | 1.00                | XML                  |
| 30-39                         | 1.04 (0.26-4.24)    | .9538               | 1.76 (0.43-7.19)    | .4299              |
| 40-49                         | 1.02 (0.26-4.08)    | .9810               | 1.72 (0.43-6.91)    | .4466              |
| 50-59                         | 0.92 (0.23-3.68)    | .9052               | 1.53 (0.38-6.16)    | .5477              |
| 60-69                         | 0.94 (0.24-3.77)    | .9309               | 1.52 (0.38-6.10)    | .5589              |
| 70-79                         | 0.99 (0.25-3.97)    | .9857               | 1.61 (0.40-6.49)    | .5065              |
| 80-89                         | 1.26 (0.31-5.13)    | .7494               | 1.88 (0.46-7.69)    | .3826              |
| >90                           | 1.46 (0.27-7.98)    | .6600               | 2.73 (0.50-14.97)   | .2484              |
| CCI score                     | XML                  | XML                  | 1.00                | XML                  |
| 0, Ref                        | 1.00                | XML                  | 1.00                | XML                  |
| 1.09 (0.90-1.09)              | .7902               | XML                  | 1.06 (0.96-1.17)    | .2566              |
| 2                             | 0.94 (0.83-1.05)    | .2656               | 1.04 (0.92-1.17)    | .5331              |
| 1.11 (0.98-1.26)              | .1066               | XML                  | 1.29 (1.13-1.48)    | .0001              |
| Alcohol consumption           | XML                  | XML                  | 1.00                | XML                  |
| No, Ref                       | 1.00                | XML                  | 1.00                | XML                  |
| Yes                           | 1.20 (1.02-1.32)    | .0246               | 1.22 (1.16-1.30)    | .0188              |
| Cigarette smoking             | XML                  | XML                  | 1.00                | XML                  |
| No, Ref                       | 1.00                | XML                  | 1.00                | XML                  |
| Yes                           | 1.42 (1.21-2.19)    | .0382               | 1.33 (1.13-1.97)    | .0224              |
| RT modality                   | XML                  | XML                  | 1.00                | XML                  |
| Non-IMRT, Ref                 | 1.00                | XML                  | 1.00                | XML                  |
| IMRT                          | 1.09 (0.61-1.94)    | .7754               | 1.18 (0.63-2.03)    | .6043              |
| RT dose, cGy                  | XML                  | XML                  | 1.00                | XML                  |
| <6000                         | 1.00                | XML                  | 1.00                | XML                  |
| 0.80 (0.60-1.07)              | .1258               | XML                  | 0.83 (0.62-1.11)    | .2059              |
| ≥6000                         | 1.0                 | XML                  | 1.0                 | XML                  |
| 2006-2010, Ref                | 0.90 (0.83-0.98)    | .0146               | 0.89 (0.81-0.97)    | .0068              |
| 2011-2014                     | XML                  | XML                  | 1.0                 | XML                  |
| AJCC clinical stage           | XML                  | XML                  | 1.0                 | XML                  |
| IA, Ref                       | 1.47 (0.73-2.96)    | .2812               | 1.42 (0.71-2.87)    | .3229              |
| IB                            | 2.90 (1.48-5.68)    | .0018               | 2.52 (1.29-5.94)    | .0075              |
| IIA                           | 3.13 (1.60-6.12)    | .0008               | 2.70 (1.37-5.31)    | .0041              |
| IIB                           | 4.41 (2.28-8.53)    | <.0001              | 3.96 (2.02-7.56)    | <.0001             |
| IIIA                          | 5.91 (3.06-11.40)   | <.0001              | 4.91 (2.51-6.60)    | <.0001             |
| IIIB                          | 7.18 (3.72-13.86)   | <.0001              | 5.82 (2.97-7.39)    | <.0001             |

Abbreviations: aHR, adjusted hazard ratio; AJCC, American Joint Committee on Cancer; CCI, Charlson comorbidity index; CCRT, concurrent chemoradiotherapy; CI, confidence interval; Ref, reference group; RT, radiotherapy.

*All variables listed in Table 1 were used in the multivariate analysis.*
2.52, 2.70, 3.96, 4.91, and 5.82 for stages IIA, IIB, IIIA, IIIB, and IIIC, respectively) (Table 2). A stratified Cox proportional-hazards model was used to analyze the mortality risk associated with different treatment modalities among patients who had TESCC in different AJCC clinical stages (Table 3). To investigate the risk of mortality after treatment, we used group 1 (surgery alone) as the control arm. After adjustment for age, sex, CCI score, clinical AJCC stage, year of diagnosis, RT modality, RT dose, alcohol consumption, and cigarette smoking, the aHRs (95% CIs) for overall mortality in clinical stages I, IIA, IIB, IIIA, IIIB, and IIIC were 2.01 (95% CI, 0.44-6.18; \( P = .3691 \)), 1.65 (95% CI, 0.99-2.70; \( P = .0575 \)), 1.48 (95% CI, 0.91-2.42; \( P = .1144 \)), 0.66 (95% CI, 1.08-1.14; \( P = .0445 \)), 0.39 (95% CI, 0.26-0.57; \( P < .0001 \)), and 0.44 (95% CI, 0.24-0.83; \( P = .0108 \)), respectively, in group 2 (trimodality therapy); and 2.06 (95% CI, 1.18-3.59; \( P = .0114 \)), 2.65 (95% CI, 1.76-4.00; \( P < .0001 \)), 2.25 (95% CI, 1.49-3.39; \( P = .0001 \)), 1.34 (95% CI, 0.79-2.28; \( P = .2786 \)), 0.82 (95% CI, 0.57-1.17; \( P = .2656 \)), and 0.93 (95% CI, 0.51-1.71; \( P = .8201 \)), respectively, in group 3 (definitive CCRT) (Table 3).

To clarify the feasible radiation dose for trimodality therapy, we used a stratified Cox proportional-hazards model to separately assess the dose levels (<6000 or ≥6000 cGy) for the risk of death and the associated irradiation doses among the patients who had TESCC in different AJCC stages and in those receiving trimodality therapy. For investigating the mortality risk after treatments, we used a radiation dose <6000 cGy as the control arm (Table 4). After adjustment for age, sex, CCI score, clinical AJCC stage, year of diagnosis, RT modality, RT dose, alcohol consumption, and cigarette smoking, the aHR for overall mortality in all stages was 1.33 (95% CI, 1.06-1.84; \( P = .0448 \)) among patients who received trimodality therapy at a dose of <6000 cGy. The aHRs for overall mortality among patients who had early clinical stage (IA-IIB) and advanced clinical stage (IIIA-IIIC) TESCC were 0.85 (95% CI, 0.26-2.7; \( P = .7816 \)) and 1.41 (95% CI, 1.01-1.98; \( P = .0481 \)), respectively, among those who received trimodality therapy at an RT dose of ≥6000 cGy.

Figure 1 presents Kaplan-Meier OS curves for the patients in the 3 treatment arms who were in different

### TABLE 3. Stratified Cox Proportional-Hazards Model For the Risk of Death and Associated Treatment Modalities Among Patients With Different American Joint Committee on Cancer Stages of Thoracic Esophageal Squamous Cell Carcinoma

| Treatment | No. of Patients | No. of Deaths | Death Rate, % | Univariate Analysis | Multivariate Analysis |
|-----------|----------------|---------------|---------------|---------------------|----------------------|
|           |                |               | HR (95% CI)   | \( P \)            | aHR (95% CI)\(^a\)  | \( P \) |
| Stage IA-IB |                |               |               |                     |                      |       |
| Surgery alone, Ref | 240 | 66 | 22.11 | 1.00 | 1.00 |
| CCRT—surgery | 190 | 42 | 33.33 | 1.47 (0.36-6.09) | .5923 | 2.01 (0.44-6.18) | .3691 |
| CCRT | 44 | 22 | 50 | 2.07 (1.23-3.47) | .0058 | 2.06 (1.18-3.59) | .0114 |
| Stage IIA |                |               |               |                     |                      |       |
| Surgery alone, Ref | 294 | 168 | 35.56 | 1.00 | 1.00 |
| CCRT—surgery | 90 | 32 | 35.56 | 1.00 | 1.00 |
| CCRT | 68 | 35 | 51.47 | 1.54 (0.95-2.49) | .0777 | 1.65 (0.99-2.70) | .0575 |
| CCRT | 136 | 101 | 74.26 | 2.69 (1.80-4.01) | < .0001 | 2.65 (1.76-4.00) | < .0001 |
| Stage IIB |                |               |               |                     |                      |       |
| Surgery alone, Ref | 365 | 179 | 31 | 1.00 | 1.00 |
| CCRT—surgery | 100 | 31 | 31 | 1.00 | 1.00 |
| CCRT | 44 | 37 | 44.58 | 1.55 (0.96-2.50) | .0712 | 1.48 (0.91-2.42) | .1144 |
| CCRT | 182 | 111 | 60.99 | 2.69 (1.71-3.81) | < .0001 | 2.25 (1.49-3.39) | < .0001 |
| Stage IIIA |                |               |               |                     |                      |       |
| Surgery alone, Ref | 714 | 454 | 53.57 | 1.00 | 1.00 |
| CCRT—surgery | 272 | 136 | 50 | 0.63 (0.37-1.07) | .0886 | 0.66 (1.08-1.14) | .0445 |
| CCRT | 414 | 303 | 73.19 | 1.29 (0.77-2.17) | .3332 | 1.34 (0.79-2.28) | .2786 |
| CCRT | 1027 | 786 | 85 | 1.00 | 1.00 |
| Stage IIIC |                |               |               |                     |                      |       |
| Surgery alone, Ref | 882 | 693 | 85 | 1.00 | 1.00 |
| CCRT | 14 | 11 | 78.57 | 1.00 | 1.00 |
| CCRT | 173 | 107 | 61.85 | 0.43 (0.23-0.79) | .0072 | 0.44 (0.24-0.83) | .0108 |
| CCRT | 695 | 575 | 82.73 | 0.89 (0.49-1.62) | .7097 | 0.93 (0.51-1.71) | .8201 |

Abbreviations: aHR, adjusted hazard ratio; CCI, Charlson comorbidity index; CCRT, concurrent chemoradiotherapy; CI, confidence interval; HR, hazard ratio; Ref, reference group; Ref, referent category; RT, radiotherapy.

\(^a\)HRs were adjusted for age, sex, CCI score, clinical American Joint Committee on Cancer stage, year of diagnosis, RT modality, RT dose, alcohol consumption, and cigarette smoking.
clinical AJCC stages. The 2-year OS rates in early clinical stages I, IIA, and IIB were 84.44%, 76.57%, and 74.37%, respectively, in group 1; 100%, 70.14%, and 59.74%, respectively, in group 2; and 69.75%, 42.24%, and 41.78%, respectively, in group 3. The OS rate in group 1 was highest among patients with early stage disease (log-rank test; \( P < .0001 \)); however, the OS rate in group 2 was highest among those with advanced-stage disease (log-rank test; \( P < .0001 \)). The 2-year OS rates in patients with advanced clinical stage IIIA, IIIB, and IIIC TESCC were 57.47%, 20.33%, and 20.17%, respectively, in group 1; 57.84%, 56.17%, and 48.77%, respectively, in group 2; and 32.85%, 22.11%, and 19.66%, respectively, in group 3.

Figure 2 illustrates Kaplan-Meier OS curves for the patients who received trimodality therapy stratified by RT dose and AJCC stage. The OS rate was the highest in the low-dose irradiation group (log-rank test; \( P = .0195 \)). The 2-year OS rates were 57.46% and 37.27% among patients who received trimodality therapy doses of \(<6000\) cGy and \(\geq 6000\) cGy, respectively. The 2-year OS rates in patients who had early clinical stage TESCC (IA-IIB) were 62.24% and 61.67% among those who received trimodality therapy doses of \(<6000\) cGy and \(\geq 6000\) cGy, respectively; and the 2-year OS rates in those who had advanced clinical stage disease (IIIA-IIIC) were 54.26% and 56.24% among those who received trimodality therapy doses of \(<6000\) cGy and \(\geq 6000\) cGy, respectively.

**DISCUSSION**

In the 1990s, trimodality therapy at various RT doses and fractionations, with different CT regimens and durations, and with miscellaneous entry criteria was evaluated in 7 trials.\(^{12-14,21-24}\) Three meta-analyses have been performed to estimate the value of trimodality therapy; among these, 2 trials indicated the survival benefit and better locoregional control of trimodality therapy over surgery alone, whereas results from the third meta-analysis were noncommittal.\(^{31-33}\) Among 3 additional modern randomized trials (French Digestive Oncology Federation [FFCD] 9901, Cancer and Leukemia Group B [CALGB] 9781, and Crohn’s Stricture Study [CROSS] trials), the FFCD 9901 trial revealed that trimodality therapy with cisplatin did not improve survival but enhanced postoperative mortality in patients with stage I or II esophageal cancer at the GE junction.\(^{15}\) In the CROSS study, weekly administrations of carboplatin and paclitaxel in trimodality therapy improved OS compared with surgery alone.\(^{5}\) In addition, only 23% of patients (\(n = 84\)) in the CROSS study had SCC (vs 100% in our study). The most recent and largest of these trials involved 12 randomized comparisons of trimodality therapy (either CCRT or sequential chemoradiation) with surgery alone for esophageal or GE junction cancer, including the FFCD 9901, CALGB 9781, and CROSS trials, which demonstrated survival benefits.\(^{34}\) Although the CALGB 9781 meta-analysis of cisplatin therapy only accrued 56 patients (the target number was 475 patients), a significant survival benefit for trimodality therapy was reported.\(^{14,34}\) In addition, the trimodality therapy assessed in most trials was CCRT, not sequential chemoradiation; however, sequential chemoradiation was used in the CALGB 9781 trial. Currently, many institutions in the United States offer trimodality therapy as an option. Nevertheless, the optimal value and applications for trimodality therapy, including RT doses, fractions, CT
Figure 1. Kaplan-Meier curves illustrate the overall survival of patients who received different treatments (surgery alone, concurrent chemoradiotherapy [CCRT] plus surgery, and CCRT alone) for thoracic esophageal squamous cell carcinoma in (A) all stages, (B) stage I, (C) stage IIA, (D) stage IIB, (E) stage IIIA, (F) stage IIIB, and (G) stage IIIC.
regimens, SCC and adenocarcinoma types, and location of esophageal cancer, remain unclear. In our current study, we enrolled homogenous patients, including those who had TESCC without adenocarcinoma or cervical or GE junction cancers and had received cisplatin-based CCRT regimens and relatively consistent RT doses and fraction sizes. Our results supply better indications for further design of randomized trials, in addition to providing more information for clinical physicians.

Although smoking and alcohol use are well known risk factors for ESCC, their roles as prognostic factors are controversial. Some studies have examined the prognostic role of smoking among patients with ESCC. According to Thrift et al and Sundelof and colleagues, smoking was independently associated with decreased survival among patients with ESCC. By contrast, Yu et al reported no association between smoking-related survival and ESCC. However, in the current study, the multivariate Cox regression analysis indicated that alcohol consumption and cigarette smoking were significant, independent predictors of a poor prognosis in patients with TESCC who were receiving treatment (Table 2). Smoking causes genetic or epigenetic alterations; modulates the expressions of large numbers of genes, including those that encode molecules related to proliferation, invasion, and metastasis; and interacts with major treatment modalities. These mechanisms might explain the effect of smoking on survival, in that smoking might alter the behavior of a tumor and promote its progression. Similarly, the association between ESCC and prediagnosed alcohol consumption is well established. However, evidence for prediagnosed alcohol consumption as a prognostic factor in patients with ESCC is insufficient. In our study, alcohol consumption was a significant, independent predictor of a poor outcome in patients with TESCC who were receiving treatments. The potential mechanisms through which alcohol consumption might influence survival include the inhibition of immune function, an increase in local permeability, and the generation of metabolites as carcinogens. Our results are also compatible with those from previous studies. By contrast, the use of surgery alone, trimodality therapy, or definitive CCRT causes side effects in cardiopulmonary functions. Patients with ESCC who have alcohol consumption and cigarettes smoking habits may have poor cardiopulmonary function and, accordingly,
cannot tolerate aggressive treatments, resulting in more complications with similar treatments.53-56

In the current study, we evaluated CCRT administered with a cisplatin-based regimen, because most practice guidelines for CCRT among patients with TESCC in Taiwan include cisplatin-based RT.1 In addition, a review from Duke University suggests no benefit from paclitaxel-based neoadjuvant CCRT over cisplatin.37 Furthermore, most recent meta-analyses have revealed a 2-year OS benefit for trimodality therapy for various CT regimens over surgery alone, although only 2 of 10 trials were individually positive.12,14,58 The CT regimens in the meta-analysis of 10 trials included paclitaxel, mitomycin, or cisplatin.58 Therefore, the true survival benefits reported in that meta-analysis were unclear in patients with esophageal cancer who were receiving trimodality therapy with various CT regimens. For our current analysis, we collected data from homogenous patients with TESCC who received only cisplatin-based CCRT.

AJCC stage IIIA is a very important cutoff point for patients with TESCC who undergo surgery alone, receive trimodality therapy, or receive CCRT. According to our data, this is because trimodality therapy was not superior to surgery alone in patients with early stage (I-IIIB) TESCC (Table 3). In multivariable analyses, trimodality therapy demonstrated survival benefits over surgery alone for patients with stage IIIA, IIIB, and IIIC disease. Moreover, in the FFCD 9901 trial, 19%, 53%, and 27% of patients had stage I, II, and III disease, respectively (all in early stages)15; thus, the trial demonstrated that, compared with surgery alone, trimodality therapy with cisplatin does not improve the survival of patients with stage I or II esophageal cancers.15 By contrast, in the CALGB 9781 and CROSS trials, there were patients who had more advanced-stage esophageal cancer, and both trials reported significantly better OS with trimodality therapy.5,14 These outcomes are compatible with our current results.

CCRT, which can preserve the esophagus, is questionable as a promising therapeutic alternative to surgery. Stage IIIA is still the important boundary for surgery alone versus definitive CCRT (Table 3). After multivariable analyses, compared with CCRT, surgery alone may have been associated with improved survival in patients with early stage (I-IIIB) TESCC (Table 3). Abrams et al also reported similar outcomes and stated that CCRT was not a suitable substitute for surgery alone in patients with early stage esophageal cancers.59 However, no statistically significant survival benefits was observed between definitive CCRT and surgery alone in patients with advanced-stage (IIA-IIIC) TESCC. Teoh and colleagues reported a randomized trial in which CRT for ESCC resulted in long-term survival comparable to that achieved with surgery, and the majority of their patients had advanced stage disease.19 A meta-analysis also indicated that the OS was equivalent between surgery alone and definitive CCRT.50 Our results do not support definitive CCRT as an alternative to surgery in the early stages of TESCC (I-IIB). However, for advanced TESCC (IIA-IIIB), definitive CCRT is an alternative to surgery alone.

Compared with adenocarcinoma, ESCC was previously considered to have a high local recurrence rate, and a higher RT dose (≥6000 cGy) may be necessary, according to Japanese studies in patients with ESCC.61-64 In addition, most studies have considered that the prognosis of adenocarcinoma is more favorable than that of SCC. In the FFCD 9901 trial, 19%, 53%, and 27% of patients who had advanced-stage TESCC (Table 4 and Fig. 2). The mechanism for this might be that, in patients with TESCC who receive trimodality therapy, higher RT doses result in increased impairment of gas exchange.53 Postoperative acute respiratory complications are more likely in patients who have lower lung volumes and lower post-CRT diffusion capacity of the lung for carbon monoxide and in those who receive higher RT doses.53 These acute respiratory complications are also associated with a significant reduction in survival among patients with TESCC.53

Trimodality therapy is an effort to reduce tumor burden, increase the rate of complete resections, eradicate micrometastases, reduce cancer cell dissemination, and prolong survival.70,71 Hence, trimodality therapy, rather than surgery alone, could be more suitable for patients with advanced-stage (IIIA-IIIC) TESCC. CCRT also might be an alternative to surgery alone in those with advanced TESCC. Nevertheless, if the patient is operable, then trimodality therapy could be the best choice for advanced TESCC (IIA-IIIC) (Table 3 and Fig. 1). The current results are compatible with those reported by Yen et al.1 In clinical practice, we suggest that surgery should be the first choice for patients who have early stage (I-IIIB) TESCC, and trimodality therapy could be beneficial for the survival of those with advanced-stage (IIA-IIIC) TESCC. The optimal RT dose in trimodality therapy should be <6000 cGy (Table 4 and Fig. 2).
This study has some limitations. First, the toxicity induced by the 3 different treatments could not be determined; therefore, the treatment-related mortality estimates may have been biased. However, previous studies reported more complications and mortality with trimodality therapy versus surgery alone.\textsuperscript{5,14,15} The survival benefits with trimodality therapy in the current study could only be underestimated. Second, because all patients with TESCC were enrolled from an Asian population, the corresponding ethnic susceptibility remains unclear; hence, our results should be cautiously extrapolated to non-Asian populations. Third, the diagnoses of all comorbid conditions were completely dependent on ICD-9-CM codes. Nevertheless, the Taiwan Cancer Registry Administration randomly reviews charts and interviews patients to verify the accuracy of the diagnoses, and hospitals with outlier chargers or practices may undergo an audit and subsequently receive heavy penalties if malpractice or discrepancies are identified. Fourth, to prevent the creation of several subgroups, various surgical procedures were not categorized separately during our analyses. Thus, the effects of different surgical procedures remain unclear. Fifth, a possible selection bias in this study might be related to the application of definitive CCRT or trimodality therapy to relatively large and unresectable TESCCs that initially had the same clinical stage. If more unresectable tumors were present or if poor response rates and pathologic features were obtained with trimodality therapy or definitive CCRT, then the survival benefit would be underestimated. However, among patients who had advanced-stage disease, the survival rate was still significantly higher for those who received trimodality therapy, and no statistical significance was observed between CCRT and surgery alone.

The conclusions of the current study could not be overturned. Therefore, for obtaining crucial information concerning population specificity and disease occurrence, a large-scale, randomized trial comparing carefully selected patients who receive suitable treatments is essential. Finally, the cancer registry database does not contain information regarding dietary habits, socioeconomic status, or body mass index, all of which may be risk factors for mortality. However, considering the magnitude and statistical significance of the observed effects in this study, these limitations are unlikely to affect the conclusions.

CONCLUSIONS

Trimodality therapy may be beneficial for the survival of patients with advanced TESCC. The optimal RT dose in trimodality therapy should be <6000 cGy. CCRT might be an alternative to surgery alone in those with advanced-stage (IIIA-IIIC) TESCC.

FUNDING SUPPORT

This work was supported by Taipei Medical University (TMU105-AE1-B26) and Wan Fang Hospital (106-eva-01).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Wei-Cheng Lin: Conception and design, collection and assembly of data, data analysis and interpretation, writing, and final approval of article. Yi-Fang Ding: Conception and design, collection and assembly of data, writing, and final approval of article. Han-Lin Hsu: Collection and assembly of data, writing, and final approval of the article. Jer-Hwa Chang: Collection and assembly of data, data analysis and interpretation, writing, and final approval of the article. Kevin Sheng-Po Yuan: Collection and assembly of data, writing, and final approval of the article. Alexander T. H. Wu: Collection and assembly of data, writing, and final approval of the article. Chia-Lun Chang: Collection and assembly of data, writing, and final approval of the article. Shee-Uan Chen: Collection and assembly of data, writing, and final approval of the article. Szu-Yuan Wu: Conception and design, collection and assembly of data, data analysis and interpretation, administrative support, writing, and final approval of the article.

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