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# Neoadjuvant Chemoradiation Versus Upfront Esophagectomy in Clinical Stage II and III Esophageal Squamous Cell Carcinoma

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## ABSTRACT

**Background.** The benefits of neoadjuvant chemoradiation (NCRT) compared to upfront esophagectomy (UE) in esophageal squamous cell carcinoma (ESCC) is controversial. Our purpose was to determine whether clinical stages based on the 8th edition American Joint Committee on Cancer Tumor-Node-Metastasis staging system could guide treatment decision.

**Methods.** Data from 2503 patients with clinical stages II and III ESCC diagnosed between 2008 and 2014 were obtained from a nationwide database. Propensity score matching was used to identify well-balanced pairs of patients. Cox proportional hazards regression and log-rank test were used in the survival analysis. The outcomes of patients receiving "NCRT followed by surgery" or "UE" strategies were compared.

**Results.** The treatment modality (UE or NCRT) was not a prognostic factor in clinical stage II ESCC (HR: 0.97; $p = 0.778$). In contrast, the UE group demonstrated a significantly worse outcome compared with the NCRT group in clinical stage III ESCC (HR: 1.39; $p < 0.001$). After matching, patients who underwent UE for clinical stage II ESCC had median survival/3-year overall survival (OS) rates of 27.8 months/39.2% compared with 32.7 months/ 49.8% in the NCRT group ($p = 0.508$). The patients who underwent UE for clinical stage III ESCC had median survival/3-year OS rates of 17.9 months/28.2% in the UE group compared with 24.0 months/41.8% in the NCRT group ($p < 0.001$).

**Conclusions.** Our data suggest that NCRT strategy improved survival compared with UE in clinical stage III ESCC but not in clinical stage II tumors.

Multidisciplinary therapy comprising surgery, chemotherapy, and radiotherapy has been widely used for the treatment of locally advanced esophageal cancer in an attempt to improve the outcomes.[1,2] A randomized trial has shown that the survival of patients with clinical stages T1N1 or T2-3N0-1 could be enhanced with the implementation of neoadjuvant chemoradiation (NCRT) compared with surgery alone.[3] However, another randomized trial demonstrated that NCRT did not improve the R0 resection rate or survival compared with surgery alone in patients with earlier stages (stage I or II) of esophageal cancer.[4] On the other hand, several retrospective or population-based studies have shown that upfront esophagectomy (UE) and adjuvant treatments guided by the pathological stages could yield outcomes comparable to those with neoadjuvant strategies in patients with clinical stage II and even stage III esophageal cancers.[5–8] Similarly, our previous studies have suggested that surgery followed by adjuvant chemoradiation (ACRT) was significantly more effective than surgery alone to increase overall survival (OS) and decrease the recurrence rates.[9–11]

With the introduction of the 8th edition of the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) Staging System, we aimed to determine whether this new edition of clinical staging could facilitate

decision-making in treatment strategies. The survival rates of patients receiving "NCRT followed by surgery" and "UE" for clinical stages II and III ESCC were compared.

## METHODS

Patient data were obtained from the Taiwan Cancer Registry (TCR) database, which is a national population-based database organized by the Health Promotion Administration and the Ministry of Health and Welfare (MOHW), Taiwan. Hospitals with more than 50 beds that provide outpatient and hospitalized cancer care are recruited to participate in reporting all newly diagnosed malignant neoplasms to the registry. There are currently more than 80 participating hospitals, which account for > 90% of the total cancer cases in Taiwan.[12] Data confidentiality was ensured by the Health and Welfare Data Science Center (HWDC) and the MOHW, Taiwan, by encrypting individual identifiers to protect the patient's privacy before releasing information to investigators for research purposes. In this study, the diagnosis of ESCC was based on the International Classification of Diseases for Oncology (ICD-O-3) site codes (C15.0–C15.5, C15.8, and C15.9) and morphology codes (8070–8076, and 8083). The cancer stage was determined based on the 8th edition of the AJCC TNM staging system.[13] Patients diagnosed with clinical stages II and III ESCC between 2008 and 2014 ($N = 6332$), and who underwent NCRT followed by surgical resection or UE (alone or with ACRT) as the initial treatment modalities ($N = 2519$) were included in the study. The patients in the UE group were further classified into "UE ± CRT" and "UE only" subgroups. The former included patients who received esophagectomy only for pT1/2N0 tumors and ACRT for higher stage tumors, based on the concept of "pathological stage-based ACRT".[14] The latter group included patients with tumor stages higher than pT1/2N0 but received surgery only without adjuvant treatment. Patients with incomplete clinicopathological information, which precluded statistical analysis, were excluded ($N = 16$). The medical information for patients including sex, date of birth, date of hospitalization, date of diagnosis, care facilities, clinical stage, surgical method, surgical margin, pathologic stage, and treatment modalities was collected from the database. Individual patient-level data were linked with the National Register of Deaths Database for confirmation of survival status and the date of death, and with the National Health Insurance database for identification of comorbidities. Charlson's comorbidity index (CCI) was calculated using the ICD-9-CM codes, excluding cancer-related diseases, in the year before starting the initial treatment.[15]

*Statistics*

Categorical and continuous variables were compared with the $\chi^2$ test and Student's $t$ test, respectively. Propensity score matching was performed to decrease the confounding effects due to the nonrandomized assignment. First, a propensity score for each patient was calculated by logistic regression using the variables of age, sex, clinical T and N categories, tumor location, differentiation grade, tumor length, and comorbidity score. Then, a 1:1 matched study group was created with the use of a greedy matching algorithm. After matching, 150 and 357 well-balanced pairs of patients with clinical stages II and III ESCC, respectively, were identified for comparison of outcomes. Univariable and multivariable survival analyses were performed using the Cox proportional hazards regression model. Survival curves were plotted using the Kaplan–Meier method and compared with the log-rank test. The OS was calculated as the period from the date of initial treatment and the date of death. Patients who survived until the end of the follow-up period (December 31, 2015) were censored. All statistical calculations were performed using the Statistical Analysis System (version 9.3; SAS Institute, Inc, Cary, NC) and the Statistical Product and Service Solutions (version 20; SPSS Inc, Chicago, IL). A $p$ value < 0.05 was considered statistically significant.

## RESULTS

Data for 2503 patients with clinical stages II ($n = 937$) and III ($n = 1566$) ESCC were collected from the TCR database. The median follow-up time for all patients was 20.1 (95% confidence interval (CI): 4.7–72.1) months and that for surviving patients was 37.8 (95% CI: 13.8–83.4) months. The clinical and pathological characteristics of the patients are shown in Tables 1 (Stage II) and 2 (Stage III).

*Clinical Stage II Patients*

Of the 937 patients with clinical stage II ESCC, 655 received UE, whereas 282 of them received NCRT followed by surgery as the initial treatment. While patients in the NCRT group had larger tumors (tumor length: 5.1 vs. 3.6 cm), patients in the UE group were older (56.1 vs. 53.8 years) and had higher CCI. Non-R0 resection was noted in 9.8% and 5.3% of patients in the UE and NCRT groups, respectively ($p = 0.032$). In the UE group, 48.1% of patients had advanced T category (pT3/4), and 37.1% had positive lymph node involvement. In contrast, 35.8% of patients in the NCRT group had no detectable tumors at the primary site, and 77% of the patients had no lymph node involvement.

**TABLE 1** Clinical and pathological characteristics of clinical stage II patients before and after propensity score matching

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | UE | NCRT | p | UE | NCRT | p |
| Total | 655 | 282 | | 150 | 150 | |
| Age, yr, mean ± SD | 56.1 ± 10.0 | 53.8 ± 8.7 | 0.001 | 54.3 ± 9.5 | 55.0 ± 8.6 | 0.538 |
| Sex (%) | | | 0.680 | | | 0.358 |
| Male | 601 (91.8) | 261 (92.6) | | 141 (94.0) | 137 (91.3) | |
| Female | 54 (8.2) | 21 (7.5) | | 9 (6.0) | 13 (8.7) | |
| Tumor length, cm, mean ± SD | 3.6 ± 2.0 | 5.1 ± 2.5 | < 0.001 | 4.7 ± 2.6 | 4.9 ± 2.5 | 0.697 |
| Location (%) | | | 0.279 | | | 0.903 |
| Upper | 78 (11.9) | 37 (13.1) | | 20 (13.3) | 20 (13.3) | |
| Middle | 249 (38.0) | 112 (39.7) | | 63 (42.0) | 57 (38.0) | |
| Lower | 235 (35.9) | 84 (29.8) | | 42 (28.0) | 45 (30.0) | |
| Unknown | 93 (14.2) | 49 (17.4) | | 25 (16.7) | 28 (18.7) | |
| Differentiation (%) | | | < 0.001 | | | 0.742 |
| Well | 21 (3.2) | 4 (1.4) | | 3 (2.0) | 4 (2.7) | |
| Moderate | 449 (68.6) | 155 (55.0) | | 105 (70.0) | 96 (64.0) | |
| Poor | 154 (23.5) | 53 (18.8) | | 30 (20.0) | 36 (24.0) | |
| Unknown | 31 (4.7) | 70 (24.8) | | 12 (8.0) | 14 (9.3) | |
| CCI (%) | | | < 0.001 | | | 0.414 |
| 0 | 354 (54.1) | 192 (68.1) | | 87 (58.0) | 95 (63.3) | |
| 1 | 195 (29.8) | 56 (19.9) | | 43 (28.7) | 33 (22.0) | |
| ≥ 2 | 106 (16.2) | 34 (12.1) | | 20 (13.3) | 22 (14.7) | |
| c T category | | | < 0.001 | | | 0.908 |
| T2 | 430 (65.7) | 123 (43.6) | | 72 (48.0) | 73 (48.7) | |
| T3 | 225 (34.4) | 159 (56.4) | | 78 (52.0) | 77 (51.3) | |
| c N category | | | 0.003 | | | 0.810 |
| N0 | 501 (76.5) | 189 (67.0) | | 95 (63.3) | 97 (64.7) | |
| N+ | 154 (23.5) | 93 (33.0) | | 55 (36.7) | 53 (35.3) | |
| p (or yp) T category (%) | | | < 0.001 | | | < 0.001 |
| T0 | – | 101 (35.8) | | – | 50 (33.3) | |
| Tis | 11 (1.7) | 5 (1.8) | | 2 (1.3) | 2 (1.3) | |
| T1 | 176 (26.9) | 42 (14.9) | | 21 (14.0) | 24 (16.0) | |
| T2 | 153 (23.4) | 60 (21.3) | | 30 (20.0) | 32 (21.3) | |
| T3 | 299 (45.7) | 71 (25.2) | | 92 (61.3) | 41 (27.3) | |
| T4 | 16 (2.4) | 3 (1.1) | | 5 (3.3) | 1 (0.7) | |
| p (or yp) N category (%) | | | < 0.001 | | | 0.003 |
| N0 | 399 (60.9) | 217 (77.0) | | 90 (60.0) | 114 (76.0) | |
| N1 | 158 (24.1) | 51 (18.1) | | 39 (26.0) | 30 (20.0) | |
| N2 | 74 (11.3) | 7 (2.5) | | 17 (11.3) | 3 (2.0) | |
| N3 | 11 (1.7) | 4 (1.4) | | 2 (1.3) | 1 (0.7) | |
| Unknown* | 13 (2.0) | 3 (1.1) | | 2 (1.3) | 2 (1.3) | |
| Margin status (%) | | | 0.032 | | | 0.008 |
| Negative (R0) | 587 (89.6) | 267 (94.7) | | 124 (82.7) | 141 (94.0) | |
| Positive (R1/2) | 64 (9.8) | 15 (5.3) | | 25 (16.7) | 9 (6.0) | |
| Unknown | 4 (0.6) | 0 | | 1 (0.7) | 0 | |

*UE* upfront esophagectomy; *NCRT* neoadjuvant chemoradiation followed by surgery; *SD* standard deviation; *CCI* Charlson's comorbidity index

**TABLE 2** Clinical and pathological characteristics of clinical stage III patients before and after propensity score matching

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | UE | NCRT | p | UE | NCRT | p |
| Total | 439 | 1127 | | 357 | 357 | |
| Age, yr, mean ± SD | 55.8 ± 10.1 | 54.5 ± 8.7 | 0.001 | 55.8 ± 10.2 | 55.4 ± 8.6 | 0.499 |
| Sex (%) | | | 0.644 | | | 0.850 |
| Male | 420 (95.7) | 1072 (95.1) | | 342 (95.8) | 343 (96.1) | |
| Female | 19 (4.3) | 55 (4.9) | | 15 (4.2) | 14 (3.9) | |
| Tumor length, cm, mean ± SD | 4.9 ± 2.2 | 5.9 ± 2.6 | < 0.001 | 5.1 ± 2.1 | 5.0 ± 2.2 | 0.830 |
| Location (%) | | | 0.007 | | | 0.919 |
| Upper | 45 (10.3) | 158 (14.0) | | 39 (10.9) | 42 (11.8) | |
| Middle | 135 (30.8) | 411 (36.5) | | 120 (33.6) | 124 (34.7) | |
| Lower | 124 (28.3) | 258 (22.9) | | 93 (26.1) | 94 (26.3) | |
| Unknown | 135 (30.8) | 300 (26.6) | | 105 (29.4) | 97 (27.2) | |
| Differentiation (%) | | | < 0.001 | | | 0.976 |
| Well | 13 (3.0) | 23 (2.0) | | 11 (3.1) | 10 (2.8) | |
| Moderate | 236 (53.8) | 498 (44.2) | | 206 (57.7) | 206 (57.7) | |
| Poor | 139 (31.7) | 228 (20.2) | | 110 (30.8) | 108 (30.3) | |
| Unknown | 51 (11.6) | 378 (33.5) | | 30 (8.4) | 33 (9.2) | |
| CCI (%) | | | < 0.001 | | | 0.849 |
| 0 | 261 (59.5) | 757 (67.2) | | 227 (63.6) | 224 (62.8) | |
| 1 | 110 (25.1) | 268 (23.8) | | 86 (24.1) | 92 (25.8) | |
| ≥ 2 | 68 (15.5) | 102 (9.1) | | 44 (12.3) | 41 (11.5) | |
| c T category | | | 0.002 | | | 0.781 |
| T1/2 | 43 (9.8) | 61 (5.4) | | 27 (7.6) | 29 (8.1) | |
| T3 | 396 (90.2) | 1066 (94.6) | | 330 (92.4) | 328 (91.9) | |
| p (or yp) T category (%) | | | < 0.001 | | | < 0.001 |
| T0 | – | 372 (33.0) | | – | 116 (32.5) | |
| Tis | 21 (4.8) | 20 (1.8) | | 8 (2.2) | 8 (2.2) | |
| T1 | 42 (9.6) | 135 (12.0) | | 27 (7.6) | 46 (12.9) | |
| T2 | 54 (12.3) | 225 (20.0) | | 46 (12.9) | 71 (19.9) | |
| T3 | 297 (67.7) | 336 (29.8) | | 252 (70.6) | 110 (30.8) | |
| T4 | 25 (5.7) | 39 (3.5) | | 24 (6.7) | 6 (1.7) | |
| p (or yp) N category (%) | | | < 0.001 | | | < 0.001 |
| N0 | 142 (32.4) | 740 (65.7) | | 108 (30.3) | 232 (65.0) | |
| N1 | 154 (35.1) | 266 (23.6) | | 127 (35.6) | 79 (22.1) | |
| N2 | 107 (24.4) | 76 (6.7) | | 93 (26.1) | 30 (8.4) | |
| N3 | 26 (5.9) | 28 (2.5) | | 25 (7.0) | 11 (3.1) | |
| Unknown* | 10 (2.3) | 17 (1.5) | | 4 (1.1) | 5 (1.4) | |
| Margin status (%) | | | 0.001 | | | 0.020 |
| Negative (R0) | 370 (84.3) | 1022 (90.7) | | 302 (84.6) | 326 (91.3) | |
| Positive (R1/2) | 65 (14.8) | 96 (8.5) | | 52 (14.6) | 30 (8.4) | |
| Unknown | 4 (0.9) | 9 (0.8) | | 3 (0.8) | 1 (0.3) | |

*UE* upfront esophagectomy; *NCRT* neoadjuvant chemoradiation followed by surgery; *SD* standard deviation; *CCI* Charlson's comorbidity index

In the survival analysis, the median survival and the 3-year OS rate were 33.9 (95% CI: 30.2–39.6) months and 48.7% in the UE group compared with 33.7 (95% CI: 26.5–45.8) months and 49.4% in the NCRT group (Fig. 1a, $p = 0.762$). Multivariable COX regression analysis (Table 3) identified female sex (HR (hazard ratio): 0.59; 95% CI: 0.40–0.88; $p = 0.009$), poor differentiation (HR: 1.38; 95% CI: 1.12–1.71; $p = 0.003$), CCI (HR: 1.11; 95%
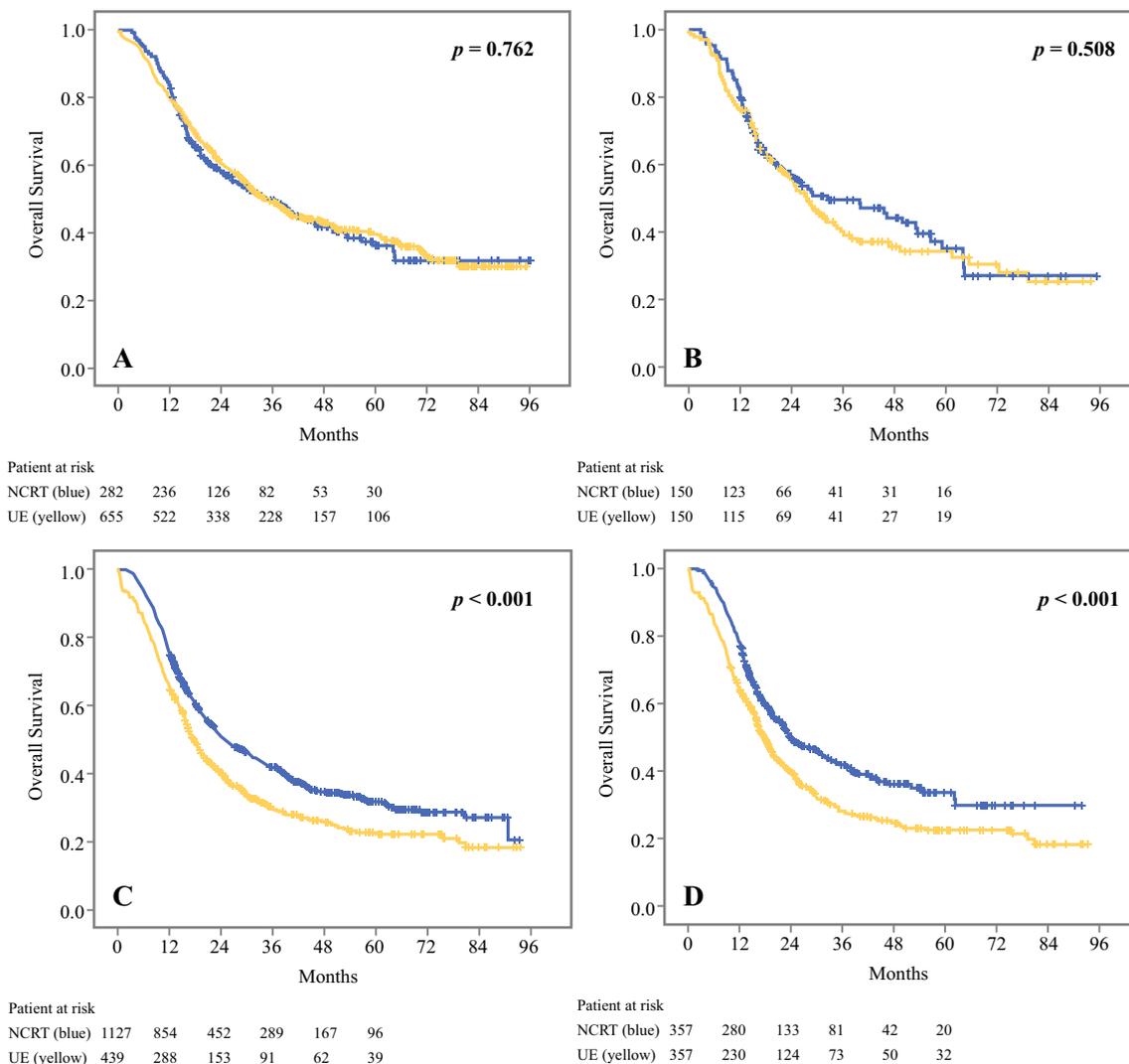
**FIG. 1** Survival curves for propensity score matched patients. Survival curves of NCRT (blue) and UE (yellow) groups with clinical stage II ESCC (**a** & **b**) before (**a**) and after (**b**) matching and with clinical stage III ESCC (**c** & **d**) before (**c**) and after (**d**) matching patients

CI: 1.02–1.20; $p = 0.015$), and positive margin (HR: 2.05; 95% CI: 1.53–2.73; $p < 0.001$) as independent prognostic factors for OS, whereas treatment modality (UE or NCRT) was not (HR: 0.97; 95% CI: 0.76–1.23; $p = 0.778$).

After propensity score matching, 150 pairs of patients with well-balanced clinical characteristics were identified for a survival analysis. The results were similar to those before matching. The median survival and 3-year OS rate were 27.8 (95% CI: 21.8–34.9) months and 39.2% in the UE group compared with 32.7 (95% CI: 21.7–53.6) months and 49.8% in the NCRT group (Fig. 1b, $p = 0.508$). There was no difference in the OS between the UE and NCRT groups. To address the possibility of decrease in power due to the reduction of sample size in clinical stage II patients after propensity score matching, we did a power analysis. Based on sample size of 300, HR of 0.97, type I error of

0.05, overall probability of event of 0.549, the power value was 0.829.

### Clinical Stage III Patients

Of the 1566 patients with clinical stage III ESCC, 439 received UE, whereas 1127 of them received NCRT followed by surgery as the initial treatment. While patients in the NCRT group had larger tumors (tumor length: 5.9 vs. 4.9 cm), patients in the UE group were older (55.8 vs. 54.5 years) and had higher CCI. Non-R0 resection was noted in 14.8% and 8.5% of patients in the UE and NCRT groups, respectively ($p = 0.001$). In the NCRT group, 33.0% of the patients had no detectable tumor at the primary site, and 65.7% of them showed negative lymph node involvement.

**TABLE 3** Multivariable Cox regression analysis for overall survival in clinical stage II and III patients
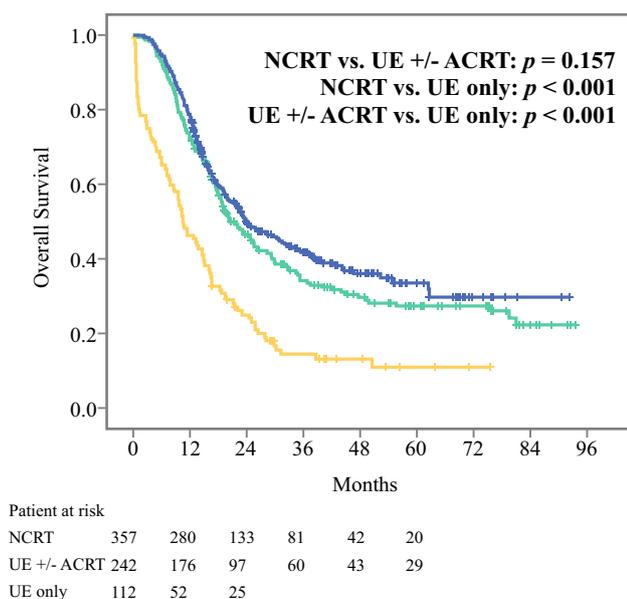
| | Clinical stage II | | Clinical stage III | |
|---|---|---|---|---|
| | HR (95% CI) | p | HR (95% CI) | p |
| Age (yr) | 1.00 (0.99–1.01) | 0.528 | 1.01 (1.00–1.02) | 0.069 |
| Sex | | | | |
| Male | 1 | | 1 | |
| Female | 0.59 (0.40–0.88) | 0.009 | 0.86 (0.60–1.24) | 0.431 |
| cT category | | | | |
| T1/2 | 1 | | 1 | |
| T3/4 | 1.17 (0.93–1.47) | 0.190 | 1.47 (1.05–2.05) | 0.024 |
| cN category | | | | |
| N0 | 1 | | – | |
| N+ | 1.04 (0.81–1.33) | 0.781 | – | |
| Location | | | | |
| Lower third | 1 | | 1 | |
| Middle third | 0.93 (0.75–1.16) | 0.526 | 0.99 (0.82–1.19) | 0.907 |
| Upper third | 0.91 (0.66–1.27) | 0.588 | 1.23 (0.97–1.56) | 0.095 |
| Differentiation | | | | |
| Good/Moderate | 1 | | 1 | |
| Poor | 1.38 (1.12–1.71) | 0.003 | 1.09 (0.91–1.31) | 0.346 |
| Tumor length (cm) | 1.00 (1.00–1.01) | 0.073 | 1.00 (1.00–1.01) | 0.003 |
| CCI | 1.11 (1.02–1.20) | 0.015 | 1.10 (1.03–1.19) | 0.009 |
| Margin status | | | | |
| Negative (R0) | 1 | | 1 | |
| Positive (R1/2) | 2.05 (1.53–2.73) | < 0.001 | 2.40 (1.95–2.94) | < 0.001 |
| Treatment strategy | | | | |
| NCRT | 1 | | 1 | |
| UE | 0.97 (0.76–1.23) | 0.778 | 1.39 (1.18–1.64) | < 0.001 |

*HR* hazard ratio; *CI* confidence interval; *CCI* Charlson's comorbidity index; *UE* upfront esophagectomy; *NCRT* neoadjuvant chemoradiation followed by surgery

In the survival analysis, the median survival and 3-year OS rate were 17.9 (95% CI: 16.0–20.0) months and 29.3% in the UE group compared with 24.8 (95% CI: 22.7–29.2) months and 41.7% in the NCRT group (Fig. 1c, $p < 0.001$). Multivariable COX regression analysis (Table 3) identified clinical category T3/4 (HR: 1.47; 95% CI: 1.05–2.05; $p = 0.024$), tumor length (HR: 1.00; 95% CI: 1.00–1.01; $p = 0.003$), CCI (HR: 1.10; 95% CI: 1.03–1.19; $p = 0.009$), positive margin (HR: 2.40; 95% CI: 1.95–2.94; $p < 0.001$), and treatment modality (UE vs. NCRT: HR: 1.39; 95% CI: 1.18–1.64; $p < 0.001$) as independent prognostic factors for OS.

After propensity score matching, 357 pairs of patients with well-balanced clinical characteristics were identified for a survival analysis. The results were similar to those before matching. The median survival and 3-year overall survival rate were 17.9 (95% CI: 15.9–20.0) months and 28.2% in the UE group compared with 24.0 (95% CI: 20.9–31.5) months and 41.8% in the NCRT group (Fig. 1d, < 0.001).

To investigate whether upfront surgery followed by adjuvant treatment could be an option for clinical stage III ESCC, the UE group was divided into "UE ± CRT" and "UE only" groups. The former included patients had ACRT for pT3/4 and/or pN + tumors, and patients had surgery only for pT1/2N0 tumors. The "UE only" included patients with pT3/4 and/or pN + tumors but without ACRT. Three patients who received ACRT for pT1/2N0 tumors were excluded from this subgroup analysis since the indication for CRT was not clear. Survival analysis showed that the median survival and 3-year overall survival rate were 20.4 (95% CI: 18.3–25.4) months and 34.1% in the UE ± CRT group compared with 10.6 (95% CI: 8.5–14.5) months and 14.5% in the UE only group ($p < 0.001$). However, the survival in the UE ± CRT group was still worse compared with that in the NCRT group, although the difference was not statistically significant (Fig. 2, $p = 0.157$).

**NCRT vs. UE +/- ACRT:** *p* = 0.157
**NCRT vs. UE only:** *p* < 0.001
**UE +/- ACRT vs. UE only:** *p* < 0.001

Patient at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| NCRT | 357 | 280 | 133 | 81 | 42 | 20 |
| UE +/- ACRT | 242 | 176 | 97 | 60 | 43 | 29 |
| UE only | 112 | 52 | 25 | | | |

**FIG. 2** Survival in patients with clinical stage III ESCC. Survival curves of NCRT (blue), UE ± CRT (green), and UE only (yellow), groups in clinical stage III patients

## DISCUSSION

Based on the TCR database, we found no significant difference in the survival of patients with clinical stage II ESCC who underwent UE versus NCRT as the initial treatment. In contrast, among patients with clinical stage III ESCC, the NCRT group was associated with better survival than the UE group. For clinical stage III ESCC, while patients receiving UE followed by pathology-based adjuvant chemoradiotherapy exhibited better survival than those receiving UE alone, their survival remained slightly inferior to that of those treated with NCRT (*p* = 0.157).

The efficacy of NCRT followed by surgery has been compared with surgery alone. In the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial, which had 81.1% of the patients with cT3 tumors and 64.5% of them with cN1 tumors, the NCRT group had a better 3-year OS compared with the surgery-alone group (58% vs. 44%, HR: 0.67).[3] In contrast, NCRT did not offer any survival benefit (3-year OS: 48% vs. 53%; HR, 0.99) in the Francophone de Cancerologie Digestive (FFCD) 9901 trial, in which 80.5% of the patients had cT1/2 tumors and 72.3% of patients had cN0 tumors.[4] Studies specific for the earlier stage, i.e., cT2N0, esophageal cancers have also demonstrated that neoadjuvant treatments confer no significant benefits on survival compared to surgery alone,[13,14] which suggested that an upfront surgical approach can be recommended for cT2N0 esophageal cancer. Our findings from the current analyses are consistent with these earlier reports and imply that while NCRT enhances survival in locally advanced (clinical stage III) esophageal cancer, its impact on early-stage (clinical stage II) tumors is less prominent. However, while previous trials compared NCRT to surgery alone, we compared NCRT to UE. In fact, 54.3% (62/114) of the patients with clinical stage II and 64.1% (200/312) with clinical stage III cancers in matched groups received ACRT for pT3/4 and/or pN + tumors. The potential effect of ACRT also was included in the analysis.

The majority of patients allocated to the upfront surgery groups in the literature received esophagectomy only. The prognostic effects of adjuvant treatments have been underestimated. Few studies have compared the outcomes of an upfront surgery followed by adjuvant treatments to those of a neoadjuvant strategy. Zahoor et al. have reported the efficacy of upfront surgery followed by pathological stage-guided adjuvant treatments.[5] In their study, adjuvant treatment was administered to 49% of upfront surgery patients, and they concluded that this strategy did not negatively influence survival compared with patients who received neoadjuvant treatments. In another study specific for clinical stage III ESCC, 45% of the patients with positive lymph node involvement after upfront surgery received adjuvant treatments.[6] The authors reported no significant differences in the survival between the "neoadjuvant chemotherapy" and "upfront surgery plus adjuvant chemotherapy for pathological positive nodal involvement" approaches. In the current study, patients who underwent UE for clinical III ESCC were further classified based on our previous work, which demonstrated the efficacy of ACRT in patients with pT3/4 and pN + ESCC.[7] The UE ± CRT group included patients who had (a) surgery for only pT1/2N0 tumors and (b) received ACRT for higher stage tumors.[7] The analysis of survival curves showed no statistically significant differences in the OS (*p* = 0.157) between UE ± CRT and NCRT groups, although the OS in the former group was slightly worse. Although the advantages of the UE approach include an accurate pathological stage assessment and potential to minimize overtreatment in patients with early-stage diseases, the UE approach may lose preemptive opportunities to eradicate systemic micrometastases early on and downstage the tumor.[5] Moreover, the potential complications and debilitation after the surgery may prevent patients from receiving adjuvant treatments. Based on our survival data and these pros and cons, we suggest NCRT as the recommended approach for clinical stage III ESCC, and ACRT can still be administered to patients following UE to enhance their survival.

Though the large size and population-based nature of the TCR database enable research focusing on ESCC, our study still has some inherent limitations. First, the detailed clinical information regarding the staging workup, chemoradiotherapy protocols, and surgical techniques was

not available. Positron emission tomography/computed tomography (PET/CT) is reimbursed by the Taiwan National Health Insurance system, and almost all patients with a diagnosis of esophageal cancer receive PET/CT as a staging workup for free. However, data regarding the irradiation field and doses are lacking. The use of endoscopic ultrasound (EUS), EUS with fine-needle aspiration has not been a routine staging modality in Taiwan. As for chemotherapy, the only regimen reimbursed by Taiwan National Insurance System is the cisplatin/5-fluorouracil-based therapy, which is frequently used preoperatively or postoperatively. With regard to surgical techniques, McKweon esophagectomy, which includes cervical esophagogastric anastomosis, is the most common procedure, given the high incidence of upper and middle third tumors in Taiwan. However, details of the extent of lymph node dissection is unavailable in this database. Second, there are no data regarding NCRT-related toxicities, its completion rates, and associated surgical complications. Patients who had tumor progression during the neoadjuvant treatments that became unresectable were not included. Similarly, any postoperative morbidity or surgical mortality, which prohibited patients from further adjuvant treatments, after the upfront surgery would be considered as "upfront surgery only." Third, all cN3M0 cancers are placed in cStage IVA based on the 8th AJCC TNM staging system. Therefore, the survival differences between UE and NCRT strategies for patients with severe lymph node involvement (cN3) by pretreatment studies were not evaluated in the current study. Finally, despite the use of propensity score matching for variables, such as age, gender, clinical tumor characteristics, and comorbidities, to identify well-balanced groups, the performance status was not included, and there might still be hidden unmeasurable factors that could have made selection bias inevitable.

## CONCLUSIONS

The treatment strategies for locally advanced ESCC were analyzed separately for clinical stages II and III tumors. While there was no significant difference in the OS between the UE and NCRT groups of patients with clinical stage II ESCC, the NCRT group was associated with better survival than the UE group in patients with clinical stage III ESCC. Our analysis demonstrated that the clinical stage of ESCC based on the 8th edition AJCC TNM staging system could facilitate patient stratification and decision-making in treatment strategies.

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