Histological Differentiation Grade and Surgery Affects Short-Term Mortality in Esophageal Squamous Cell Carcinoma Patients

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Research article

Keywords: histological differentiation grade, esophageal squamous cell carcinoma, surgery, radiotherapy, short-term mortality

DOI: https://doi.org/10.21203/rs.3.rs-33271/v1

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Abstract

Background: This study aimed to examine the relationship between the clinicopathological features, nutritional and inflammatory status, type of treatment, and short-term mortality in esophageal squamous cell carcinoma (ESCC) patients.

Methods: 205 patients with ESCC were included. The following malnutrition and inflammation criteria at the time of diagnosis were applied: body mass index < 18.5 kg/m², serum albumin level < 3.5 g/dL, neutrophil-to-lymphocyte ratio (NLR) > 3.5, platelet-to-lymphocyte ratio (PLR) > 17 and C-reactive protein. Clinicopathological features, Malnutrition status, inflammatory condition and the type of treatment were analyzed for 3-month and 6-month mortality rates by univariate and multivariate analysis.

Results: The 3-month and 6-month mortality rates were 13.2% and 27.3%, respectively. The multivariate logistic regression model after adjustment for clinicopathological variables and comorbid status found that surgery and histological differentiation grade were prognostic factors for short-term mortality.

Conclusions: In addition to surgery, histological differentiation grade independently contributes to high short-term mortality of ESCC patients.

Introduction

Esophageal cancer (EC) is the fifth leading cause of cancer-related deaths in males worldwide [1] and in Taiwan [2]. Squamous cell carcinoma and adenocarcinoma are the two major histological subtypes of EC, with different epidemiology, pathophysiology, tumor biology and prognosis [3]. Thus, their distinct clinical features should be examined separately.

In Taiwan and Asia, esophageal squamous cell carcinoma (ESCC) is the most common histological type and the major risk factors include tobacco smoking, alcohol consumption, hot food intake, family cancer history and poor nutrition, such as a lack of fruit and vegetables in the diet [4]. Additional factors reported to be associated with ESCC prognosis and survival include tumor stage, location and size, presence of localized lymphovascular invasion and distant metastasis, exposure to substances, and malnutrition [5–8].

The impact of histological differentiation grade on survival remained debated. Some studies reported that surgically resected ESCC patients with poor histological differentiation had a poor outcome [5, 6, 9], while some trials failed to detect this difference [8, 10]. These studies mainly focused on the long-term survival effects of tumor differentiation, but not on the short-term mortality rates, such as the 3-month and 6-month mortality rates following treatment completion. In locally advanced ESCC patients undergoing concurrent chemoradiotherapy (CCRT), those with a poorly differentiated histology appeared to have higher local failure rates [11]. Conversely, some reports showed that poorly differentiated ESCC patients had a better response to neoadjuvant CCRT [12] and benefited from postoperative CCRT with regard to controlling local recurrence and distant metastases [13]. Hence, it is worthwhile to examine the
possible differential effects of histological grade on short-term survival outcome when considering therapeutic strategies for ESCC.

On a different note, the relationship between pre-treatment nutrition status and clinical prognosis in ESCC is debated. First, some studies showed that body mass index (BMI) had an impact on survival in ESCC [14, 15], whereas another study found that BMI has no prognostic value for treatment outcomes [16]. Further, albumin level and weight loss are often used to evaluate the malnutrition status, but the results are not consistent [14–16]. Additionally, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were significantly predictive of poor prognosis of EC patients [17–22]. However, few studies have investigated the specific effects of these nutritional/inflammatory markers on ESCC prognosis [21, 23]. Finally, most studies addressed the relationship between pre-treatment nutrition index and overall survival [17–21]. The effect of pre-treatment nutrition status on short-term mortality of ESCC patients remains unknowns.

Taken together, the aim of this retrospective study is to analyze the effect of patient-related clinicopathologic features, pre-treatment nutritional and inflammatory status, and treatment strategies on short-term mortality rates of ESCC.

**Materials And Methods**

**Study participants**

We retrospectively reviewed medical records of 212 patients who had been diagnosed with ESCC at Chang Gung Memorial Hospital (CGMH) in Keelung (Taiwan), between January 2007 and December 2012. Seven patients were excluded due to incomplete clinicopathological data. We collected data and analyzed the following parameters: age, sex, body height, body weight, BMI, tumor location, histological differentiation grading, Charlson comorbidity index (CCI), tumor node metastasis (TNM) stage, hemoglobin level (Hb), white blood cell (WBC) count, C-reactive protein (CRP), treatment strategy, and 3-month and 6-month mortality rates.

All patients were histological proven to be ESCC. Tumors were reclassified retrospectively according to the 7th edition of the American Joint Committee on Cancer Staging System (AJCC) through comprehensive stage workups including physical examination, routine laboratory tests, chest radiography, abdominal ultrasound, bone scintigraphy, chest computed tomography, and positron emission tomography. The histological differentiation grade was assessed using the World Health Organization criteria. The pathological diagnoses and histologic grades, as well as tumor stages, were reviewed and confirmed by the esophageal cancer committee at our institute. The committee members included two thoracic surgeons, two medical oncologists, one radiation oncologist, one nuclear medicine physician, and one pathologist. This study protocol (Institutional Review Board approval number: 201600554B0) was approved by a local research ethics committee at the CGMH in Taiwan.

**Measurements of Anthropometric and Clinical Variables**
BMI, NLR, and PLR were defined as follows. BMI was calculated as the ratio of the patient’s weight to the height squared (kg/m$^2$). NLR was calculated as the ratio of absolute neutrophil count to lymphocyte count. PLR was calculated as the ratio of platelet count to lymphocyte count.

CCI was recorded to assess the severity of comorbidities [24]. Participants were considered smokers if they currently smoked tobacco or had smoked in the past. Participants were considered alcoholic drinkers if they reported consuming alcohol four or more times per week. Participants were considered as betel quid users if they reported using this substance during the previous year. Co-existing cancer was defined as the occurrence of a second primary malignancy at the time of ESCC diagnosis or months or years after ESCC was diagnosed and treated.

Treatment strategy records, including surgery, radiotherapy and chemotherapy, were retrieved for analysis. Surgical intervention was curative-intent esophagectomy with lymph node dissection. Chemotherapy was triweekly chemotherapy regimen (cisplatin, 50–75 mg/m$^2$ on day 1 and 5-fluorouracil, 600–1000 mg/m$^2$ on days 1–4). Radiotherapy with a radiation dose of 50 to 72 grays was given.

Mortality rates for 3 months and 6 months were defined as the percentage of patients dying of any cause within 90 and 180 days of treatment initiation, respectively. Treatment initiation was used as the reference date due to variation in time taken for stage work-ups.

**Statistical analysis**

Statistical analyses were performed using SPSS statistical package version 22 (SPSS, Inc., Chicago, IL, USA). In Table 1, multiple comparisons between the following factors were performed by: analysis of variance using Bonferroni adjustments (for age, BMI, CCI, Hb, WBC, albumin, CRP, PLR, and NLR) or Chi-square test for sex, tumor location, T classification, N classification, histologic differentiation grade, co-existing cancer status, smoking, alcohol consumption, betel quid use, treatment modality, treatment regimen, and prognostic outcome (3-month and 6-month mortality rates). For the univariate analyses of Table 2, Chi-square test was used to determine the association of age, sex, tumor stage, location, histologic differentiation, co-existing cancer, smoking, alcohol consumption, betel quid use, BMI, albumin, PLR, and NLR between the two groups; independent Student’s t-test (two-tailed) was used to determine the differences in CCI, Hb, WBC, total protein and CRP between the two groups. All independent variables at least marginally associated with the 3-month and 6-month mortality rates ($P \leq .2$) were included in the multiple logistic regression analysis. Independent variables marginally associated with overall survival ($P \leq .2$) were included in Cox regression analysis. A $P < .05$ was considered significant.
# Table 1
Clinical characteristics of 205 ESCC patients stratified by clinical TNM stage

| Variables expressed as number (%) or mean ± SD | All   | Stage I | Stage II | Stage III | Stage IV | \(P^*\) value |
|-----------------------------------------------|-------|---------|----------|-----------|----------|---------------|
| Patient number (%)                           | 205 (100) | 9 (4.4) | 31 (15.1) | 100 (48.8) | 65 (31.7) |               |
| Sex                                           | 188:17 | 9:0     | 27:4     | 92:8      | 60:5     | 0.632         |
| Age (years)                                   | 55.6 ± 16.4 | 60.7 ± 11.4 | 60.6 ± 12.4 | 57.8 ± 13.1 | 57.9 ± 11.5 | 0.711         |
| Tumor location                                | 49:107:49 | 2:2:5  | 4:17:10  | 28:55:17  | 15:33:17 | 0.092         |
| T classification                              | 44 (21.7):161 (78.3) | 9 (100.0):0 (0.0) | 20 (64.5):11 (35.5) | 6 (6.0):94 (94.0) | 9 (14.3):56 (85.7) | <0.001*       |
| N classification                              | 156 (76.1):49 (23.9) | 9(100.0):0 (0.0) | 31 (100.0):0 (0.0) | 64 (64.0):36 (36.0) | 52 (80.0):13 (20.0) | <0.001*       |
| Histologic differentiation grade             |       |         |          |           |          |               |

ESCC, esophageal squamous cell carcinoma; BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; WBC, white blood cell; OP, surgery; RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

\(P^*\) value for multiple comparisons was determined by ANOVA using Bonferroni adjustments for age, BMI, CCI, Hb, WBC, albumin, CRP, PLR and NLR; Chi-square test for sex, tumor location, T classification, N classification, histological differentiation grade, co-existing cancer status, smoking exposure, alcohol consumption, betel quid use, treatment modality, treatment regimen, and 3-month mortality rate and 6-month mortality rates.
| Variables expressed as number (%) or mean ± SD | All | Stage I | Stage II | Stage III | Stage IV | P*value |
|---|---|---|---|---|---|---|
| Well-: moderately -: poorly differentiated | 6:135:64 | 0:7:2 | 2:18:11 | 4:66:27 | 0:44:24 | 0.744 |
| Charlson comorbidity index (CCI) | 3.8 ± 2.0 | 4.4 ± 3.3 | 4.3 ± 2.0 | 3.7 ± 1.9 | 3.6 ± 1.8 | 0.312 |
| Co-existing cancer (%) | 40 (19.5) | 2 (22.2) | 8 (25.8) | 19 (19.0) | 11 (16.9) | 0.424 |
| Smoking (%): Alcohol (%): Betel nut (%) | 88.3:88.8:3 | 88.9:88.9:3 | 83.9:80.6:3 | 92.0:90.0:4 | 92.3:90.8:3 | 0.670 |
| BMI (kg/m²) at diagnosis | 20.7 ± 3.4 | 20.5 ± 3.2 | 20.5 ± 4.5 | 21.3 ± 5.7 | 21.0 ± 4.7 | 0.811 |
| Hb (g/dL) | 12.1 ± 2.5 | 12.4 ± 1.4 | 12.0 ± 2.0 | 11.8 ± 2.9 | 12.7 ± 2.3 | 0.361 |
| WBC (cells/µL) | 7.5 ± 4.0 | 8.5 ± 4.5 | 7.7 ± 3.3 | 7.3 ± 4.2 | 7.9 ± 4.1 | 0.668 |
| Albumin (g/dL) | 3.5 ± 1.7 | 3.6 ± 1.5 | 3.4 ± 0.8 | 3.6 ± 1.7 | 3.5 ± 0.6 | 0.097 |
| CRP (mg/dL) | 52.4 ± 37.6 | 19.8 ± 27.9 | 85.3 ± 97.6 | 44.8 ± 59.9 | 48.8 ± 64.9 | 0.392 |
| PLR | 17.8 ± 28.3 | 17.6 ± 18.4 | 22.6 ± 60.6 | 16.5 ± 25.9 | 18.7 ± 19.7 | 0.698 |
| NLR | 4.6 ± 5.5 | 3.4 ± 2.2 | 6.4 ± 15.6 | 4.2 ± 3.6 | 4.5 ± 4.6 | 0.532 |

ESCC, esophageal squamous cell carcinoma; BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; WBC, white blood cell; OP, surgery; RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

*P value for multiple comparisons was determined by ANOVA using Bonferroni adjustments for age, BMI, CCI, Hb, WBC, albumin, CRP, PLR and NLR; Chi-square test for sex, tumor location, T classification, N classification, histological differentiation grade, co-existing cancer status, smoking exposure, alcohol consumption, betel quid use, treatment modality, treatment regimen, and 3-month mortality rate and 6-month mortality rates.
## Variables expressed as number (%) or mean ± SD

|                | All        | Stage I | Stage II | Stage III | Stage IV | $P^*$value |
|----------------|------------|---------|----------|-----------|----------|------------|
| OP (%)         | 84 (40.9)  | 6 (66.7)| 18 (58.1)| 45 (45.0) | 15 (23.1)| 0.001*     |
| RT (%)         | 161 (78.5)| 2 (22.2)| 23 (74.2)| 91 (91.0) | 45 (69.2)| < 0.001*   |
| CT (%)         | 166 (80.9)| 2 (22.2)| 20 (64.5)| 90 (90.0) | 54 (83.0)| < 0.001*   |

### Treatment regimen

| Treatment regimen                                      | All        | Stage I | Stage II | Stage III | Stage IV | $P^*$value |
|--------------------------------------------------------|------------|---------|----------|-----------|----------|------------|
| No treatment (%)                                       | 3 (1.4)    | 0 (0.0) | 0 (0.0)  | 0 (0.0)   | 3 (1.4)  | 0.088      |
| Single treatment modality (OP, RT, or CT alone)      | 28 (13.7)  | 2 (22.2)| 4 (12.9) | 4 (4.0)   | 18 (27.7)| < 0.001*   |
| Preoperative CCRT followed by OP                      | 72 (35.1)  | 2 (22.2)| 13 (41.9)| 51 (51.0) | 6 (9.2)  | < 0.001*   |
| Primary CCRT                                           | 102 (49.8)| 5 (55.6)| 14 (45.2)| 45 (45.0) | 38 (58.4)| 0.358      |
| 3-month mortality rate (%)                            | 27 (13.2)  | 0 (0.0) | 5 (16.1)| 7 (7.0)   | 15 (23.1)| 0.015*     |
| 6-month mortality rate (%)                            | 56 (27.3)  | 0 (0.0) | 6 (19.4)| 18 (18.0) | 32 (49.2)| < 0.001*   |

ESCC, esophageal squamous cell carcinoma; BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; WBC, white blood cell; OP, surgery; RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

$P$ value for multiple comparisons was determined by ANOVA using Bonferroni adjustments for age, BMI, CCI, Hb, WBC, albumin, CRP, PLR and NLR; Chi-square test for sex, tumor location, T classification, N classification, histological differentiation grade, co-existing cancer status, smoking exposure, alcohol consumption, betel quid use, treatment modality, treatment regimen, and 3-month mortality rate and 6-month mortality rates.
Table 2
Univariate and multivariate analysis of factors associated with 3-month and 6-month mortality rates of 205 ESCC patients

| Prognostic factors | 3-month mortality rate | 6-month mortality rate |
|--------------------|------------------------|------------------------|
|                    | Univariate analysis    | Multivariate analysis  |
|                    | OR (95% CI) P value    | OR (95% CI) P value    | OR (95% CI) P value |
| Sex (ref: male)    | 0.43 (0.05–3.37) 0.419 | 0.16 (0.02–1.20) 0.074 |
| Age (ref: ≥65 years) | 0.91 (0.37–2.24) 0.838 | 0.49 (0.26–0.94) 0.030* |
| Tumor stage (ref: 1 + 2) | 1.31 (0.42–4.06) 0.637 | 2.39 (0.95–6.07) 0.066 |
| T classification (ref: T1-2) | 1.61 (0.52–4.93) 0.408 | 1.83 (0.79–4.24) 0.157 |
| N classification (ref: N0-1) | 0.69 (0.25–1.94) 0.483 | 0.83 (0.39–1.73) 0.611 |
| Location (ref: middle) | 1.01 (0.44–2.33) 0.983 | 0.59 (0.31–1.10) 0.097 |

ESCC, esophageal squamous cell carcinoma; BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; WBC, white blood cell; OP, surgery; RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy

*denotes $P < .05$
|                        | 3-month mortality rate | 6-month mortality rate |
|------------------------|------------------------|------------------------|
| **Histological**       |                        |                        |
| differentia-           | 0.33 (0.14–0.77)       | 0.47 (0.25–0.88)       |
| tion grade (ref:       | 0.010*                | 0.019*                |
| poorly differen-       | (0.17–0.99)            | (0.24–0.97)            |
| tiation)               | 0.047*                | 0.040*                |
|                        |                        |                        |
| **CCI** (ref: <5)      | 1.33 (0.57–3.15)       | 1.75 (0.93–3.31)       |
|                        | 0.511                  | 0.084                  |
|                        |                        |                        |
| **Co-existing cancer** | 0.90 (0.32–2.56)       | 0.76 (0.35–1.66)       |
| (ref: no)              | 0.849                  | 0.489                  |
|                        |                        |                        |
| **Smoking (%)** (ref:  | 3.00 (0.39–23.4)       | 3.84 (0.87–17.1)       |
| no)                    | 0.294                  | 0.077                  |
|                        |                        |                        |
| **Alcohol (%)** (ref:  | 0.69 (0.22–2.22)       | 0.75 (0.30–1.85)       |
| no)                    | 0.537                  | 0.534                  |
|                        |                        |                        |
| **Betel nut (%)** (ref: | 0.60 (0.24–1.50)       | 0.52 (0.26–1.02)       |
| no)                    | 0.273                  | 0.056                  |
|                        |                        |                        |
| **Hb (g/dL)** (ref: <  | 0.44 (0.19–1.03)       | 0.66 (0.35–1.25)       |
| 12)                    | 0.059                  | 0.203                  |
|                        |                        |                        |
| **WBC (cells/µL)** (ref: | 0.25 (0.07–0.89)       | 0.343 (0.11–1.11)      |
| <4000)                 | 0.032*                | 0.075                  |

ESCC, esophageal squamous cell carcinoma; BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; WBC, white blood cell; OP, surgery; RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy

*denotes \( P < .05 \)
### Results

A total of 205 ESCC patients were analyzed (Table 1). ESCC occurred predominantly in Taiwanese men aged 32 to 89 years (average age: 55.6 years). Eighty percent of the patients had an advanced TNM stage (stages III and IV). More than half of ESCC cases occur in the middle third of the esophagus. Most of the ESCC patients had an advanced tumor status (T3-4, 78.3%) and low regional lymph node involvement (N0-1, 76.1%). Two-thirds of ESCC cases had moderate tumor differentiation (65.8%). These patients had moderate comorbidities (CCI: 3.8 ± 2.0). One-fifth of ESCC patients developed other primary cancers, which most commonly occurred in the hypopharynx (28.3%), followed by the tonsils (15.6%) and tongue (10.7%). Ninety percent of ESCC patients were smokers or alcoholic drinkers, and 40% of patients were betel quid users. The BMI, Hb, WBC, albumin levels of all participants were normal at the time of diagnosis, while CRP was extraordinarily higher than normal (< 5 mg/dL).

|                                  | 3-month mortality rate | 6-month mortality rate |
|----------------------------------|------------------------|------------------------|
| **Albumin (ref: ≥ 3.5 g/dL)**    | 2.00 (0.86–4.67)       | 1.43 (0.76–2.67)       |
|                                  | 0.108                  | 0.268                  |
| **CRP (mg/dL)**                  | 1.00 (0.98–1.01)       | 1.00 (0.99–1.01)       |
|                                  | 0.56                   | 0.775                  |
| **PLR (ref: > 17)**              | 0.80 (0.28–2.27)       | 0.92 (0.44–1.94)       |
|                                  | 0.680                  | 0.832                  |
| **NLR (ref: > 3.5)**             | 0.94 (0.39–2.24)       | 1.22 (0.64–2.31)       |
|                                  | 0.885                  | 0.543                  |
| **Treatment regime**             |                        |                        |
| **OP (ref: no)**                 | 0.29(0.10–0.79)        | 0.25(0.12–0.53)        |
|                                  | 0.015*                 | < 0.001*               |
|                                  | 0.11(0.02–0.45)        | 0.002*                 |
|                                  | 0.001*                 | 0.14(0.05–0.37)        |
|                                  | 0.001*                 |                        |
| **CCRT (ref: no)**               | 0.33 (0.04–2.59)       | 0.23 (0.04–1.39)       |
|                                  | 0.327                  | 0.245                  |

ESCC, esophageal squamous cell carcinoma; BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; WBC, white blood cell; OP, surgery; RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy

*denotes $P < .05$
When patients were stratified by TNM stage, results showed that those with an advanced tumor stage had the highest mortality rates (Table 1). The aforementioned clinicopathological variables, nutrition and inflammation parameters showed no significant difference among various stages, except T and N classifications (Table 1). We applied the different malnutrition and inflammation standards previously reported to evaluate ESCC prognosis on all patient groups, and found that 40 (19.5%) had a BMI of <18.5 kg/m², 83 (40.4%) had an albumin level of <3.5 g/dL, 76 (37.0%) had an NLR of >3.5, and 62 (30.2%) had a PLR of >17. [20, 21, 25]. However, the malnutrition and inflammation rates obtained by different standards showed no significant difference at various tumor stages (data not shown).

We found that more early-stage patients received surgery (stage I: 66.7%, stage II: 58.1%), whereas a significantly higher number of advanced-stage patients received radiotherapy (stage III: 91.0%, stage IV: 69.2%) or chemotherapy (stage III: 90.0%, stage IV: 83.0%) than early-stage ones. 174 (84.9%) patients received two (CCRT, 49.8%) or more (preoperative CCRT followed by surgery, 35.1%) treatment modalities. The 3-month, and 6-month mortality rates were 13.2% and 27.3%, respectively. The major causes of 3-month and 6-month mortality rates were the same: cancer progression (68.8% and 70.1%, respectively), followed by severe infection (21.8% and 18.3%, respectively) and myocardial infarction (3.1% and 5.0%, respectively).

We performed univariate and multivariate logistic regression models and demonstrated that having undergone surgery and histologic differentiation grade significantly contributed to the 3-month and 6-month mortality rates of ESCC patients (Table 2).

**Discussion**

To better understand the prognostic role of various factors in esophageal cancer, this study recruited 205 ESCC patients and simultaneously analyzed the effects of tumor features, clinicopathologic parameters, nutritional status, inflammatory condition and treatment modality on the short-term mortality of ESCC patients. Our results demonstrated that histological differentiation grade, having undergone surgery and radiotherapy were prognostic factors for 3-month and 6-month mortality rates.

Short-term mortality is one of suitable assessment of treatment response and treatment-related complications. In the current study, poor differentiation grade independently contributed to higher short-term mortality, mostly due to cancer progression. We, thus, proposed that histologic differentiation grade is likely related with ESCC aggressiveness and its responsiveness to treatment. The expression of certain genes governing ESCC differentiation may support this [26, 27]. Activin A, a member of the transforming growth factor β superfamily, is highly correlated with differentiation degree. Surgically resected ESCC patients expressing higher tissue Activin A level had more features of poor histological differentiation and lower recurrence-free rate [27]. A member of the E2 promoter binding protein family called E2F5 is also involved with ESCC differentiation. Poorly differentiated ESCC patients who underwent curative resection had a higher tissue expression of E2F5 and a worse prognosis [26]. Tissue hypoxia may drive tumor cells to be poorly differentiated through hypoxia-inducible factor (HIF) activation [28]. This activation process...
decreases KLF-4 (Krüppel-like factor 4) expression, which is substantially associated with poor
differentiation of ESCC [29]. Ping et al further found ESCC patients with HIF-1α overexpression failed to
respond to CCRT [30]. Taken together, in ESCC patients, differentiation-associated genes that coordinate
tissue hypoxia tend to induce poor differentiation of tumor cells and make them less responsive to
treatment.

Surgery currently remains as the standard treatment for ESCC. Cochrane meta-analysis [31] found that
the short-term mortality rates were lower in the non-surgical group compared with the surgical group in a
fixed-effect model, but it was not significant in a random effects model and; therefore, CCRT might be
equivalent to surgery when analyzing survival of ESCC patients. Our results, nonetheless, showed that a
significant proportion of early-stage (stage I and II) patients underwent surgery and near half of the
advanced stage (stage III and IV) patients had CCRT. Surgery, and not CCRT, was an independent
prognostic factor for short-term mortality in ESCC patient. The analysis performed in these studies,
including ours, is at a high risk of bias due to the heterogeneity of the patients studied, the varied
treatment schedules, and the different endpoint assessment [31]. Even though salvage surgery after
CCRT is comparable with neoadjuvant CCRT followed by surgery, the residual cancer cells that had been
treated with definitive CCRT seemed to be more biologically aggressive, leading to a poorer survival
compared with recurrent cancer [32]. Therefore, well-designed trials enrolling patients with homogenous
clinical features and using the same treatment protocol to study the effect of surgery versus non-surgical
treatment on short-term mortality are necessary; otherwise, the prognostic factors based on current
evidence must be interpreted and taken with caution.

Some study limitations and intriguing observations merit further discussion. This was a retrospective,
single-institution study; therefore, inherent selection bias is inevitable, and data were not necessarily
collected from the same date, although most were taken within 2 weeks from diagnosis. Due to the
limited number of cases, we were unable to analyze the factors pertaining to the mortality outcomes of
different subgroups such as surgery alone, preoperative CCRT followed by surgery, and definitive CCRT.
Further, poorly differentiated ESCC may have a differential response to CCRT. Since radiation sensitivity is
high among undifferentiated cells that exhibit high mitotic activity and stay in the active developmental
stage [33], poorly differentiated ESCC are more susceptible to radiation [12]. In contrast, tumor cells tend
to be poorly differentiated under hypoxic conditions, which makes cells less vulnerable to radiation and
chemotherapy via HIF activation [28, 30, 34, 35]. Hence, the effect of poorly differentiated ESCC on short-
term mortality rates may be the result of their responsiveness to CCRT.

**Conclusion**

In conclusion, our study demonstrated that histological grade surgery and were independent prognostic
factors for short-term mortality of ESCC patients.

**Abbreviations**
EC: esophageal cancer; ESCC: esophageal squamous cell carcinoma; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; CRP: C-reactive protein; BMI: body mass index; CCI: Charlson comorbidity index; CCRT: concurrent chemoradiotherapy

**Declarations**

**Ethics approval and consent to participate**

This study protocol (Institutional Review Board approval number: 201600554B0) was approved by a local research ethics committee at the CGMH in Taiwan and was waived signed informed consent since the study was based on existing databases.

**Consent for publication**

Not applicable

**Availability of data and materials**

The data that support the findings of this study are available from database of the Chang Gung Memorial Hospital, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available upon reasonable request and with permission of the Chang Gung Memorial Hospital.

**Competing interests**

The authors declare no conflict of interest in employment (other than primary affiliations), grants, other commercial research support, ownership interest, consultant/advisory board, or honoraria from speakers’ bureau.

**Funding**

None.

**Acknowledgements**

This study was supported by grants (CGRPG2F0061 and CMRPG2J0041) from the Chung Gang Memorial Hospital, Keelung (Taiwan).

**Authors’ contributions**

Kun-Yun Yeh was in charge of study design, data confirmation and revision in the entire manuscript. Hsuan-Chih Kuo analyzed the original data and wrote the draft of the entire manuscript. Yi-Ping Pan collected demographic data and prepared the first draft of manuscript. Ting-You Hsu analyzed the data and made Table 1. Jui-Ying Lin analyzed the data and made Table 2. Dr. Wen-Chi Chou provided...
scholarly interpretation in short-term mortality data. Dr. Chien-Hong Lai was in charge of esophageal cancer committee and revised part of discussion. Dr. Pei-Hung Chang revised the final version in introduction and discussion. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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