Factors Predicting Effectiveness of Neoadjuvant Therapy for Esophageal Squamous Cell Carcinoma

Yu Ohkura, MD, Masaki Ueno, MD, PhD, Toshiro Iizuka, MD, Shusuke Haruta, MD, PhD, Tsuyoshi Tanaka, MD, PhD, and Harushi Udagawa, MD, PhD

Abstract: The aim of the study was to elucidate pretreatment factors that can predict the outcome of neoadjuvant chemoradiotherapy or chemotherapy (NAC(R)T) and help us choose treatment strategies appropriate for individual patients.

Few studies have investigated whether clinical data obtainable before the treatment can predict the efficacy of NAC(R)T. Of 1540 patients treated for esophageal squamous cell carcinoma (ESCC) at our department between January 2000 and June 2014, those who underwent surgical resection of cStage II or more advanced ESCC after NAC(R)T (113 NACRT and 146 NACT patients) were enrolled in this study. Information all available before the treatment was analyzed to extract factors that can predict the effectiveness of NAC(R)T. NAC(R)T was considered effective when Grade 2 or greater treatment efficacy was achieved based on the histological grading system.

NACRT was effective in 51 (45%) of 113 patients. The analysis of 35 pretreatment factors showed that female sex (hazard ratio [HR] = 3.650; 1.181–11.236), absence of dyslipidemia (HR = 3.284; 1.341–8.041), and histologically poorly differentiated tumor (HR = 2.431; 1.052–5.619) were factors predicting NACRT effectiveness. On the other hand, NACT was effective in 21 (14%) of 146 patients. The analysis of pretreatment factors showed that absence of dyslipidemia (HR = 10.204; 1.302–83.33) and therapy with docetaxel, cisplatin, and 5-fluorouracil (HR = 2.097; 1.027–4.280) were factors predicting NACT effectiveness.

The findings of this study investigating factors that could predict the outcome of NAC(R)T suggest that the prevalence of dyslipidemia influences the outcome of NAC(R)T for ESCC.

(Medicine 95(15):c3365)

Abbreviations: DCF = docetaxel + cisplatin + 5FU, ESCC = Esophageal squamous cell carcinoma, FAP = 5FU + doxorubicin + cisplatin, FP = 5FU + cisplatin, NACRT = neoadjuvant chemoradiotherapy, NACT = neoadjuvant chemotherapy.

INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) is the most dangerous form of gastrointestinal cancer.1,2 As the first report of its efficacy in the 1980s,3–6 chemoradiotherapy (CRT) has been used widely to treat ESCC. Findings from the histopathological examination of esophageal cancer resected after CRT are extremely useful in judging CRT efficacy and selecting additional therapies and consequently in predicting the prognosis.7,8 Several studies investigated the predictors of post-CRT prognosis,9–11 whereas others analyzed pretreatment imaging findings and histopathological findings to reveal the predictors of CRT efficacy.12–16 As in CRT, several studies reported the efficacy of neoadjuvant chemotherapy (CT), making it standard treatment for esophageal cancer.17–21 However, except the studies using pretreatment imaging findings, no studies used pretreatment factors such as patient background and hematological findings to predict the outcomes of NAC(R)T. The discovery of pretreatment clinical or biopsy findings that can predict or enhance the efficacy of CRT or CT would enable us to establish more effective and individualized treatment strategies. In this study, we assessed the independent factors that can predict the outcome of NAC(R)T (hereinafter, CRT/CT-effectiveness) applied to the patients with ESCC.

MATERIAL AND METHODS

Patients

Of 1540 patients treated for esophageal cancer at our hospital between January 2000 and June 2014, 113 patients with cStage II or above ESCC who had undergone CRT as the first therapy and then esophageal resection were enrolled in this study. Neoadjuvant CT regimens in the CRT protocol were high-dose FP (800 mg/m² 5-fluorouracil [FU], 80 mg/m² cisplatin) in 28 patients; low-dose FP (200 mg/m² 5FU, 4 mg/m² cisplatin) in 66; and docetaxel, cisplatin, and 5-fluorouracil (DCF) (60 mg/m² docetaxel, 50 mg/m² cisplatin, 500 mg/m² FU) in 19. The dose of radiation was >50 Gy and ≤50 Gy in 11 and 102 patients, respectively. Data obtainable before therapy were analyzed to extract factors predicting CRT effectiveness.

Similarly, 146 patients who had undergone esophageal resection after NACT were analyzed to reveal factors that can predict efficacy specific to CT. Neoadjuvant CT regimens in this group were high dose FP (800 mg/m² 5FU, 80 mg/m² cisplatin) in 95 patients; DCF (60 mg/m² docetaxel, 50 mg/m² cisplatin, 500 mg/m² FU) in 38; and FAP (600 mg/m² FU, 30 mg/m² doxorubicin, 60 mg/m² cisplatin) in 13.

Methods

The analysis items were 35 factors (10 pre-treatment patient background factors, 18 pre-CRT biochemical factors, 5 tumor factors, and 2 treatment factors) and 33 factors in total (10 pre-treatment patient background factors, 18 pre-CT biochemical factors, 4 tumor factors, and 1 treatment factor) were analyzed to extract factors predicting NACRT and NACT
In our hospital, the tumor grading was performed in accordance with American Joint Committee on Cancer (AJCC) guidelines. C(R)T was considered to be effective when the resected specimen was diagnosed to show Grade 2 or greater treatment effect by histopathological assessment. The histopathological effects of NAC(R)T were defined according to the Japanese Classification of Esophageal Cancer, 10th edition. The grading systems—Grade 0: ineffective, no recognizable cytological or histological therapeutic effect. Grade 1: slightly effective, apparently viable cancer cells account for 1/3 or more of the tumor tissue, but there is some evidence of degeneration of the cancer tissue or cells. Grade 1a: viable cancer cells accounting for 1/3 or more, but <2/3, of tumor tissue. Grade 2: moderately effective, viable cancer cells account for <1/3 of the tumor tissue, whereas the other cancer cells are severely degenerated or necrotic. Grade 3: markedly effective, no viable cancer cells are evident. In this study, the routine pathology was performed by multiple pathologists. However, in our hospital, a single chief pathologist reviewed all pathological materials and routinely made a definitive diagnosis of the histopathological response grade 0 to 3 of NACRT or NACT. This study was approved by the Institutional Review Board of our hospital.

**Statistics**

Cumulative overall survival (OS) was analyzed by the Kaplan–Meier method. A difference between 2 groups was analyzed using the Chi-square and Mann–Whitney U tests, and multiple regression analysis was used to reveal factors predicting C(R)T effectiveness. All variables with significance of $P < 0.10$ in the simple Cox proportional hazards models were entered into multiple Cox proportional hazards models. In multiple Cox proportional hazards models, $P < 0.05$ was considered significant. Statistical analysis was performed using the SPSS ver.19 (SPSS Inc., Chicago, IL), with significance set at $P < 0.05$. Staging was performed in accordance with the Union for International Cancer Control TNM Classification of Malignant Tumors (version 7).

**RESULTS**

**Overall Survival of Patients who Underwent NAC(R)T**

The overall survival curves of patients who underwent NACRT or NACT are shown in Figure 1. NAC(R)T, when resulted in downstaging due to tumor shrinkage and achieved Grade 2 or greater treatment efficacy based on the histological grading system, increasing survival rates were revealed. The actuarial survival rates of patients who underwent NACRT with a histological grade 2 or greater (5-year survival, 76 %) were significantly ($P < 0.001$) higher than those of patients with a histological grade of 0–1 (5-year survival, 34 %). On the other hand, the actuarial survival rates of patients who underwent NACRT with a histological grade 2 or greater (5-year survival, 94 %) were significantly ($P = 0.010$) higher than those of patients with a histological grade of 0 to 1 (5-year survival, 63 %).

**Factors Predicting NACRT Effectiveness**

We first examined 113 patients who had undergone NACRT at our hospital and revealed that 51 (45 %) patients had achieved Grade 2 or greater treatment efficacy using the histological grading system for post-treatment evaluation. The univariate analysis between 62 patients with a histological grade of 0 to 1 and 51 patients with a grade of 2 or greater showed a significant difference in 3 factors: female sex, absence of dyslipidemia, and poorly differentiated tumor (Table 1). Patients had been defined as having dyslipidemia when hematological findings showed $\geq 140$ mg/dL of LDL-cholesterol, $<40$ mg/dL of HDL-cholesterol, or $\geq 150$ mg/dL of triglycerides. This study included patients who had been undergoing drug therapy for dyslipidemia.

Multivariate analysis was performed using the results of the univariate analysis (Table 2). The selected variables were age, female sex, CRP value, absence of dyslipidemia, and poorly differentiated tumor. It revealed that female sex (male/female = 94/19, HR = 3.650), absence of dyslipidemia (positive/negative = 39/74, HR = 3.284), and histologically...
poorly differentiated tumor (well to moderately/poorly differentiated = 71/42, OR = 2.431) were all independent factors predicting NACRT effectiveness.

Factors Predicting NACRT Effectiveness

We then examined 146 patients who had undergone NACT at our hospital and revealed that 21 (14%) patients had postoperatively achieved Grade 2 or above treatment efficacy. The univariate analysis between 125 patients with a histological grade of 0–1 and 21 patients with a grade of 2 or above showed

| TABLE 1. Patient Characteristics and the Results of Univariate Analysis of the Factors Predicting NACRT Effectiveness |
|---------------------------------------------------------------|-------------------|-----------------|-----------------|-----------------|
|                                                          | Total: n = 113 n (%) | Grade 0–1 (n = 62) | Grade 2 or Above (n = 51) | P Value |
| Patients characteristics                                    | or Median          | CRT Effectiveness |
| Age                                                          | 63.6 (40–84)       | 63.5 (40–84)      | 64.0 (40–77)    | 0.372 |
| Sex (male/female)                                           | 94/19              | 56/6             | 38/13           | 0.025 |
| PS (0–1/2–)                                                 | 69/44              | 36/26            | 33/18           | n.s. |
| Brinkman index (<600/≥600)                                  | 50/63              | 27/35            | 23/28           | n.s. |
| Heart disease                                               | 13 (11.5%)         | 56/6             | 44/7            | n.s. |
| Pulmonary disease                                           | 11 (9.7%)          | 57/5             | 45/6            | n.s. |
| Hypertension                                                | 24 (21.2%)         | 51/11            | 38/13           | n.s. |
| Diabetes mellitus                                           | 15 (13.3%)         | 52/10            | 46/5            | n.s. |
| Dyslipidemia                                                | 39 (34.5%)         | 35/27            | 39/12           | 0.026 |
| BMI (<25/≥25)                                               | 100/13             | 48/8             | 43/5            | n.s. |
| Pre-CRT hematological items                                 |                    |                  |                 |       |
| WBC (×10³/mL)                                               | 6.8                | 6.6              | 6.9             | n.s. |
| Hb (g/dl)                                                   | 13.6               | 13.7             | 13.6            | n.s. |
| Pt (×10³/mL)                                                | 249                | 240.0            | 254.0           | n.s. |
| TP (g/dL)                                                   | 7.3                | 7.3              | 7.4             | n.s. |
| Alb (g/dL)                                                  | 3.8                | 3.8              | 3.8             | n.s. |
| Cre (mg/dL)                                                 | 0.7                | 0.7              | 0.7             | n.s. |
| ALT (IU/L)                                                  | 15.0               | 16.0             | 14.0            | n.s. |
| LDH (IU/L)                                                  | 156.0              | 156.5            | 151.1           | n.s. |
| ALP (IU/L)                                                  | 204.0              | 209.0            | 204.0           | n.s. |
| CRP (mg/dL)                                                 | 0.3                | 0.3              | 0.4             | 0.072 |
| Na (mmol/L)                                                 | 141.0              | 141.0            | 141.0           | n.s. |
| K (mmol/L)                                                  | 4.4                | 4.3              | 4.4             | n.s. |
| Ca (mmol/L)                                                 | 9.3                | 9.4              | 9.3             | n.s. |
| HbA1c (%)                                                   | 5.6                | 5.6              | 5.6             | n.s. |
| CEA (µg/L)                                                  | 2.4                | 2.5              | 2.4             | n.s. |
| CA19–9 (U/mL)                                               | 11.0               | 11.0             | 10.0            | n.s. |
| SCC (µg/L)                                                  | 1.1                | 1.0              | 1.2             | n.s. |
| CYFRA (µg/L)                                                | 1.9                | 1.6              | 2.0             | n.s. |
| Tumor factors                                               |                    |                  |                 |       |
| 18F-FDG accumulation (SUV max)                              | 13.7               | 12.7             | 13.7            | n.s. |
| cT1-3/cT4                                                   | 65/48              | 38/24            | 27/24           | n.s. |
| cNO1-cN2                                                    | 75/38              | 41/21            | 34/17           | n.s. |
| cStage -3a/3b-                                              | 42/71              | 20/42            | 22/29           | n.s. |
| Well-moderate/poor                                          | 71/42              | 44/18            | 27/24           | 0.048 |
| Treatment factors                                           |                    |                  |                 |       |
| high FP/low FP/DCF                                          | 28/66/19           | 14/35/13         | 14/31/6         | n.s. |
| Radiation dose (≤50/≥50 Gy)                                 | 102/11             | 54/8             | 48/3            | n.s. |

Alb = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, BMI = body mass index, CEA = carcinoembryonic antigen, Cre = creatinine, CRP = C-reactive protein, CRT = chemoradiotherapy, CYFRA = cytokeratin-19 fragments, DCF = docetaxel + cisplatin + 5FU, FDG = fluoro-D-glucose, FP = 5FU + cisplatin, Hb = hemoglobin, LDH = lactate dehydrogenase, NACRT = neoadjuvant chemoradiotherapy, Pt = platelet count, SCC = squamous cell carcinoma, TP = total protein, WBC = white blood cell.

| TABLE 2. Results of Multivariate Analysis of the Factors Predicting NACRT Effectiveness |
|---------------------------------------------------------------|-------------------|-----------------|-----------------|-----------------|
|                                                          | P Value | Hazard Ratio | 95% CI |
| Sex (male/female)                                           | 0.025   | 3.650        | 1.181–11.236   |
| Dyslipidemia                                                | 0.009   | 3.284        | 1.341–8.041    |
| Well-moderate/poor                                          | 0.038   | 2.431        | 1.052–5.619    |

CI = confidence interval, NACRT = neoadjuvant chemoradiotherapy.

Factors Predicting NAC(T) Effectiveness

We then examined 146 patients who had undergone NACT at our hospital and revealed that 21 (14%) patients had postoperatively achieved Grade 2 or above treatment efficacy. The univariate analysis between 125 patients with a histological grade of 0–1 and 21 patients with a grade of 2 or above showed
a significant difference in 2 factors: absence of dyslipidemia and DCF therapy (Table 3).

Multivariate analysis was performed using the results of the univariate analysis (Table 4). The selected variables were age, sex, absence of dyslipidemia, and DCF. It showed that absence of dyslipidemia (positive/negative = 43/103, HR = 10.204) and DCF (HR = 2.097) were both independent factors predicting NACT effectiveness.

DISCUSSION
In general, a postoperative increase in survival rates among patients treated with NACRT or NACT is attributed to the tumor-shrinking effect of NAC(R)T.4–11 In a study of esophageal resection after CRT, Swisher et al reported that 3-year survival rates were significantly higher among patients who had smaller remnant tumors in postoperative histopathological examination.8 In addition, Law et al showed that pN0, female

### TABLE 3. Patient Characteristics and the Results of Univariate Analysis of the Factors Predicting NACT Effectiveness

| Patients characteristics | Total: n = 146 n (%) | CT-Effectiveness |  |  |
|---------------------------|----------------------|-----------------|---|---|
|                           | or Mean              | Grade0–1: n = 125 | Grade2–: n = 21 | P  |
| Age                       | 63.0 (37–79)         | 63.0 (37–79)    | 66.0 (51–76) | 0.867. |
| Sex (male/female)         | 131/15               | 111/14          | 20/1          | 0.328. |
| PS (0–1/2–)               | 78/68                | 66/59           | 12/9          | n.s.  |
| Brinkman Index (< 600/≥600) | 55/91              | 44/81           | 11/10         | n.s.  |
| Heart disease             | 9 (6.1 %)            | 117/8           | 20/1          | n.s.  |
| Pulmonary disease         | 27 (18.5 %)          | 103/22          | 16/5          | n.s.  |
| Hypertension              | 35 (24.0 %)          | 95/30           | 16/5          | n.s.  |
| Diabetes mellitus         | 14 (9.6 %)           | 113/12          | 19/2          | n.s.  |
| Dyslipidemia              | 43 (29.5%)           | 83/42           | 20/1          | 0.004 |
| BMI (<25/≥25)             | 131/15               | 111/14          | 20/1          | n.s.  |

Prechemotherapy hematological items

|                           | Total: n = 146 n (%) | CT-Effectiveness |  |  |
|---------------------------|----------------------|-----------------|---|---|
|                           | or Mean              | Grade0–1: n = 125 | Grade2–: n = 21 | P  |
| WBC (×10³/mL)             | 6.2                  | 6.2             | 5.9 | n.s.  |
| Hb (g/dl)                 | 14.0                 | 13.9            | 14.2 | n.s.  |
| Plt (×10³/mL)             | 238.0                | 241.0           | 227.0 | n.s.  |
| TP (g/dL)                 | 7.3                  | 7.3             | 7.5 | n.s.  |
| Alb (g/dL)                | 4.0                  | 4.0             | 4.0 | n.s.  |
| Cre (mg/dL)               | 0.8                  | 0.8             | 0.8 | n.s.  |
| ALT (IU/L)                | 14.0                 | 14.0            | 15.0 | n.s.  |
| LDH (IU/L)                | 172.0                | 172.0           | 169.0 | n.s.  |
| ALP (IU/L)                | 200.5                | 202.0           | 196.0 | n.s.  |
| CRP (mg/dL)               | 0.1                  | 0.1             | 0.1 | n.s.  |
| Na (mmol/L)               | 141.0                | 141.0           | 140.0 | n.s.  |
| K (mmol/L)                | 4.3                  | 4.3             | 4.2 | n.s.  |
| Ca (mmol/L)               | 9.3                  | 9.3             | 9.3 | n.s.  |
| HbA1c (%)                 | 5.6                  | 5.6             | 5.6 | n.s.  |
| CEA (µg/L)                | 2.6                  | 2.6             | 2.5 | n.s.  |
| CA19-9 (U/mL)             | 11.0                 | 11.0            | 8.0 | n.s.  |
| SCC (µg/L)                | 1.2                  | 1.2             | 1.2 | n.s.  |
| CYFRA (µg/L)              | 1.3                  | 1.3             | 1.3 | n.s.  |

Tumor factors

|                      | Total: n = 146 n (%) | CT-Effectiveness |  |  |
|----------------------|----------------------|-----------------|---|---|
|                      | or Mean              | Grade0–1: n = 125 | Grade2–: n = 21 | P  |
| cT1–3/cT4            | 142/4                | 121/4           | 21/0 | n.s.  |
| cN0–1/cN2–           | 95/51                | 80/45           | 15/6 | n.s.  |
| cStage -3a/3b-       | 104/42               | 89/36           | 15/6 | n.s.  |
| Well-moderate/poor   | 107/39               | 91/34           | 16/5 | n.s.  |

Treatment factors

|                      | Total: n = 146 n (%) | CT-Effectiveness |  |  |
|----------------------|----------------------|-----------------|---|---|
|                      | or Mean              | Grade0–1: n = 125 | Grade2–: n = 21 | P  |
| FP/DCF/FAP           | 95/38/13             | 88/25/12        | 7/13/1 | <0.001 |

BMI = body mass index, CRT = chemoradiotherapy, DCF = docetaxel+ cisplatin+ 5FU, FAP = 5FU+ doxorubicin+ cisplatin, FDG = fluoro-d-glucose, FP = 5FU+cisplatin, NACT = neoadjuvant chemotherapy.

### TABLE 4. Results of Multivariate Analysis of the Factors Predicting NACT-Effectiveness

|               | P Value | Hazard Ratio | 95% CI |
|---------------|---------|--------------|--------|
| Dyslipidemia  | 0.027   | 10.204       | 1.302–83.33 |
| FP/DCF/FAP    | 0.042   | 2097         | 1.027–4.280 |

CI = confidence interval, DCF = docetaxel+ cisplatin+ 5FU, FAP = 5FU+ doxorubicin+ cisplatin, FP = 5FU+cisplatin, NACT = neoadjuvant chemotherapy.
sex, and R0 were statistically significant good prognostic factors.3 According to Schneider et al10 and Okumura et al,11 after R0 resection surgery, prognosis was significantly better among patients with resected tumors or with N0 classification.

In the present study also, NAC(R)T, when resulted in downstaging due to tumor shrinkage and achieved Grade 2 or greater treatment efficacy based on the histological grading system, increasing survival rates were revealed. These findings therefore showed that it is highly feasible to predict the outcome of NAC(R)T preoperatively. If such prediction is possible, we can select therapy that is more suitable to each patient. In this study, we therefore investigated pretreatment factors associated with the tumor-shrinking effects of NAC(R)T and revealed that factors predicting NAC(R)T effectiveness were female sex, absence of dyslipidemia, and histologically poorly differentiated tumor, whereas factors predicting NACT effectiveness were the absence of dyslipidemia and DCF therapy.

To date, several studies have reported imaging findings as the predictors of the effectiveness of CRT.11–16 According to Owaki et al, endoscopic ultrasound performed before and early after CRT predicted treatment outcome accurately with sensitivity of 85% and specificity of 95%, which was comparable with histopathological evaluations.14 In addition, Okumura et al performed preoperative combination examination of esophagography and endoscopy and showed that combination examination predicted histopathological outcomes with >80% accuracy.13 However, these studies predicted histopathological treatment outcome using imaging data obtained before and after CRT, but real prediction based solely on patient background factors, biochemical data, or preoperative evaluation items which are available before the treatment is started, has not been performed. Other studies performed positron emission tomography-computed tomography before treatment to show the correlation between the accumulation of fluoro-D-glucose (FDG) and the histological grading of treatment outcome.13–16 However, no correlation between the preoperative accumulation of FDG and histopathological findings was observed in the database at our hospital. In this study, we therefore used only pretreatment factors such as patient background, pre-CRT biochemical data, and tumor and treatment factors to reveal factors associated with Grade 2 or above treatment outcome. As shown in Tables 1 and 2, female sex, poorly differentiated tumor, and absence of dyslipidemia were the factors predicting the efficacy of CRT.

However, no previous study has shown that CRT is more effective in female than in men. In this study, the rate of smoking was significantly lower in female patients than in male patients (P < 0.001), and first of all, this might have been a reason for female sex being a significant factor even though the Brinkman index which was included in the initial patient factors was not the factor predicting the CRT effectiveness. The Brinkman Index was obtained using the following equation: number of cigarettes smoked per day × number of years smoked.29 Smoking is known to induce systemic hypoxia which decreases the radiosensitivity of cells as well as tumors.28–31 In addition, nicotine was reported to induce radioresistance.35 Therefore, a higher smoking rate in our male patients than in female patients may have contributed to the suppression of CRT efficacy because of a reduction in radiosensitivity due to hypoxia and an increasing radioresistance due to nicotine. Second, female hormone estrogens have beneficial effects on plasma lipid and lipoprotein concentrations and reduce arteriosclerosis extent on a number of animal models.36–38 Although the arteriosclerotic disease generally increase significantly after menopause, the incidence of arteriosclerotic disease among female was much lower until at least age 75.39,40 In this study, the age of the patients were around 60; therefore, the risk of arteriosclerosis of the female patients is lower than male patients. A relation between arteriosclerosis and treatment resistance is indicated on the following paragraph. In this regard, however these 2 reasons are only a hypothesis thoroughly. If we can accumulate more cases, a more precise analysis might show strong similarities.

The Bergonie–Tribondeau’s law, which was proposed by Bergonie and Tribondeau in 1906, states that the sensitivity toward radiation is high among tissues with a large proportion of morphologically and functionally undifferentiated cells, high mitotic activity, and a long and active developmental stage.25 Since then, many studies have investigated radiosensitivity in humans.42–44 In the present study, we revealed poorly differentiated tumor as a factor significantly influencing the efficacy of CRT. Poorly differentiated cells have high mitotic activities compared with well-differentiated ones, and tumors containing a large proportion of poorly differentiated cells have a high degree of malignancy but are more susceptible to radiation.

A novel finding of this study is that the prevalence of dyslipidemia affects the efficacy of NAC(R)T. We can guess arteriosclerosis is strongly related between the efficacy of NAC(R)T and dyslipidemia. In the past reports, it is well known that the arteriosclerosis is strongly associated with dyslipidemia.45–47 As arteriosclerosis progresses, tumor tissue becomes more hypoxic and phenotypically more malignant, enhancing its resistance toward CT and CRT.29–34 Basic research showed that the adaptor protein p66Shc, which is normally located adjacent to the insulin receptor, plays a significant role in dyslipidemia and arteriosclerosis and, through its expression, increases cellular resistance toward radiotherapy and chemotherapy.25,48 This suggests that patients with dyslipidemia may develop resistance toward radiotherapy and chemotherapy, thereby compromising the tumor-shrinking effect of (R)T, because of tumor hypoxia enhanced by arteriosclerosis and the expression of p66Shc. Our study is the first clinical, but not basic, study to report similar findings.

The limitation of this study was possible bias in the selection of surgery and neoadjuvant therapy because this was a retrospective study of NAC(R)T. The treatment applied is rather heterogeneous. NACT is the standard treatment for advanced esophageal carcinoma (e.g., cStage II or above) in our hospital. On the other hand, there is a tendency to indicate NACRT in patients with relatively advanced cancer (particularly, in T factors). In fact, NACT is an accepted standard of treatment with locally advanced esophageal cancer. In addition, this study enrolled patients with esophageal cancer who had successfully undergone surgery after NACRT, indicating that these patients had relatively good general conditions and cancer had progressed only up to a certain point. Furthermore, at our hospital, we tend to select DCF therapy for patients with highly advanced cancer, indicating that clinical stage is less severe in patients undergoing NACT with FP than those undergoing NACT with DCF. Finally, no review pathology was performed, but routine pathology assessed in this study.

CONCLUSIONS

The findings of this study revealed that female sex, absence of dyslipidemia, and poorly differentiated tumor are the predictors of NAC(R)T efficacy, with the absence of dyslipidemia also being a significant factor for NACT. The
elucidation of clinicopathological factors that can predict the outcome of neoadjuvant therapy will help us establish a more effective treatment plan for each patient.

REFERENCES

1. Napier KJ, Scheerer M, Misra S. Esophageal cancer: a review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol. 2014;6:112–120.

2. Matsuhashi D, Uenoisono Y, Arigami T, et al. Clinical significance of circulating tumor cells in peripheral blood of patients with esophageal squamous cell carcinoma. Ann Surg Oncol. 2015;22:3674–3680.

3. Kato K, Muro K, Minashi K, et al. Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for stage II–III esophageal squamous cell carcinoma. JCOG Trial (JCOG 9906). 2011;81:684–690.

4. Natsugoe S, Okumura H, Matsumoto M, et al. Randomized controlled study on preoperative chemoradiotherapy followed by surgery versus surgery alone for esophageal squamous cell cancer in a single institution. Dis Esophagus. 2006;19:468–472.

5. John MJ, Flam MS, Mowry PA, et al. Radiotherapy alone and chemoradiation for nonmetastatic esophageal carcinoma. A critical review of chemoradiation. Cancer. 1989;63:397–403.

6. Li X, Zhao LJ, Liu NB, et al. Feasibility and efficacy of concurrent chemoradiotherapy in elderly patients with esophageal squamous cell carcinoma: a respective study of 116 cases from a single institution. Asian Pac J Cancer Prev. 2015;16:1463–1469.

7. Swisher SG, Hofstetter W, Wu TT, et al. Proposed revision of the esophageal cancer staging system to accommodate pathologic response (pP) following preoperative chemoradiation (CRT). Ann Surg. 2005;241:810–817.

8. Law S, Kwong DL, Wong KH, et al. The effects of neoadjuvant chemoradiation on pT/NM staging and its prognostic significance in esophageal cancer. J Gastrointest Surg. 2006;10:1301–1311.

9. Naunheim KS, Petruska P, Roy TS, et al. Neoadjuvant chemoradiation therapy for esophageal squamous cell carcinoma. J Thorac Cardiovasc Surg. 1992;103:887–893.

10. Schneider PM, Baldus SE, Metzger R, et al. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. Ann Surg. 2005;242:684–692.

11. Okumura H, Uchikado Y, Matsumoto M, et al. Prognostic factors in esophageal squamous cell carcinoma patients treated with neoadjuvant chemoradiation therapy. Int J Clin Oncol. 2013;18:329–334.

12. Owaki T, Matsumoto M, Okumura H, et al. Endoscopic ultrasonography is useful for monitoring the tumor response of neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma. Am J Surg. 2012;203:191–197.

13. Okumura H, Natsugoe S, Yokomukara N. The new criteria of clinical response for the primary tumor based on the findings of histological response after chemoradiation therapy in esophageal cancer. Jpn J Gastroenterol Surg. 2005;38:1637–1644.

14. Atsumi K, Nakamura K, Abe K, et al. Prediction of outcome with FDG-PET in definitive chemoradiotherapy for esophageal cancer. J Radiation Res. 2013;54:890–898.

15. Flanagan GL, Dehdashi F, Siegal BA, et al. Staging of esophageal cancer with 18F-fluorodeoxyglucose positron emission tomography. Am J Roentgenol. 1997;168:417–424.

16. Couper GW, McAteer D, Wallis F, et al. Detection of response to chemotherapy using positron emission tomography in patients with esophageal and gastric cancer. Br J Surg. 1998;85:1403–1406.

17. William HA, Sally PS, John B, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 1987;27:5062–5067.
38. Wagner JD. Effects of sex steroid treatment on the cardiovascular system. *Infertility Reprod Med Clin N Am.* 2001;12:511–533.

39. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham Study. *N Engl J Med.* 1984;311:1144–1147.

40. Kinjo K, Kimura Y, Shinzato Y, et al. An epidemiological analysis of cardiovascular diseases in Okinawa, Japan. *Hypertens Res.* 1992;15:111–119.

41. Bergonie J, Tribondeau L. De quelques resultats de la radiotherapie et essai de fixation d’une technique rationnelle. *Comptes Rendus des Seances de l’Academie des Sciences.* 1906;143:983–985.

42. van der Meer Y, Huiskamp R, Davids JA, et al. The sensitivity of quiescent and proliferating mouse spermatogonial stem cells to X irradiation. *Radiat Res.* 1992;130:289–295.

43. Potten CS, Booth C. The role of radiation-induced and spontaneous apoptosis in the homeostasis of the gastrointestinal epithelium: a brief review. *Comp Biochem Physiol B Biochem Mol Biol.* 1997;118:473–478.

44. Bergonie J, Tribondeau L. Interpretation of some results of radiotherapy and an attempt at determining a logical technique of treatment. *Radiat Res.* 1959;11:587–588.

45. Tanaka A. Postprandial hyperlipidemia and atherosclerosis. *J Atheroscler Throm.* 2004;11:322–329.

46. Kameda K, Matsuzawa Y, Kubo M, et al. Increased frequency of lipoprotein disorders similar to type III hyperlipoproteinemia in survivors of myocardial infarction in Japan. *Atherosclerosis.* 1984;51:241–249.

47. McNamara JR. Remnant like particle (RLP) cholesterol is an independent cardiovascular disease risk factor in women: results from the Framingham Heart Study. *Atherosclerosis.* 2001;154:229–236.

48. Napoli C, Martin-Padura I, de Nigris F, et al. Deletion of the p66Shc longevity gene reduces systemic and tissue oxidative stress, vascular cell apoptosis, and early atherogenesis in mice fed a high-fat diet. *Proc Natl Acad Sci.* 2005;100:2112–2116.

49. Kasuno K, Yoshida H, Irani K. P66 Shc: senescence accelerator? I DO NOT need it. *Kiso Rouka Kkenkyuu.* 2009;33:17–22.