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Original Article

The predictive value of histological tumor regression grading (TRG) for therapeutic evaluation in locally advanced esophageal carcinoma treated with neoadjuvant chemotherapy

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Abstract

Response criteria remain controversial in therapeutic evaluation for locally advanced esophageal carcinoma treated with neoadjuvant chemotherapy. We aimed to identify the predictive value of tumor regression grading (TRG) in tumor response and prognosis. Fifty-two patients who underwent neoadjuvant chemotherapy followed by esophagectomy and radical 2-field lymphadenectomy between June 2007 and June 2011 were included in this study. All tissue specimens were reassessed according to the TRG scale. Potential prognostic factors, including clinicopathologic factors, were evaluated. Survival curves were generated by using the Kaplan-Meier method and compared with the log-rank test. Prognostic factors were determined with multivariate analysis by using the Cox regression model. Our results showed that of 52 cases, 43 (83%) were squamous cell carcinoma and 9 (17%) were adenocarcinoma. TRG was correlated with pathologic T ($P = 0.006$) and N ($P < 0.001$) categories. Median overall survival for the entire cohort was 33 months. The 1- and 2-year overall survival rates were 71% and 44%, respectively. Univariate survival analysis results showed that favorable prognostic factors were histological subtype ($P = 0.003$), pathologic T category ($P = 0.026$), pathologic N category ($P < 0.001$), and TRG G0 ($P = 0.041$). Multivariate analyses identified pathologic N category ($P < 0.001$) as a significant independent prognostic parameter. Our results indicate that histomorphologic TRG can be considered as an alternative option to predict the therapeutic efficacy and prognostic factor for patients with locally advanced esophageal carcinoma treated by neoadjuvant chemotherapy.

Key words Tumor regression grading, esophageal cancer, neoadjuvant chemotherapy, efficacy assessment

Esophageal carcinoma is a common malignant tumor. Surgical resection and reconstruction is a major treatment for this type of cancer. Because of the application of comprehensive therapy and advancements in surgical techniques, the clinical efficacy on esophageal cancer has been greatly improved. The 5-year survival rate remains between 15% and 39%[1]. A recent study indicated that the 5-year survival rate of patients with stage I esophageal cancer was approximately 60%–80%; however, for patients with locally advanced esophageal carcinoma (stage III), this rate dropped to less than 25%[2]. Hence, preoperative neoadjuvant chemotherapy or chemoradiotherapy combined with surgery have gained more attention in the treatment of locally advanced esophageal cancer[3,4].

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Nevertheless, accurate evaluation of the efficacy of neoadjuvant therapy is a challenge in esophageal carcinoma treatment. The esophagus is a cavitary organ. The morphology of esophageal tumors is irregular, and uneven tumor regression has been noted after treatment. In addition, pathologic T category of esophageal cancer is determined by the depth of tumor infiltration rather than tumor length[5]. Thus, although Response Evaluation Criteria in Solid Tumors (RECIST) is currently used to determine solid tumor response to chemotherapy[6,7], these criteria are not ideal for assessing the response of esophageal carcinoma to neoadjuvant chemotherapy.

Here, the percentage of residual cancer cells, that is, tumor regression grading (TRG), was used to evaluate the efficacy of neoadjuvant therapy on esophageal carcinoma. TRG was first proposed in the National Comprehensive Cancer Network (NCCN) guidelines (second edition) for gastroesophageal junction tumors in 2011. Standards for TRG are hotly debated. For example, some scholars categorize TRG into three grades[8,9], whereas others indicate that there are four[9]. Likewise, some studies suggest that the extent of proliferation in the fibrous tissue of lesions should be regarded as an evaluation criterion[10], whereas others do not [8,9,11]. Study samples in current investigations are limited to cases treated with neoadjuvant chemoradiotherapy, in which the fibrosis degree after neoadjuvant chemoradiotherapy was more severe than that after neoadjuvant chemotherapy. Thus, the value of histological TRG in evaluating the efficacy of neoadjuvant chemotherapy remains to be elucidated. This retrospective study was designed to determine the clinical significance and prognostic value of histological TRG and to screen prognostic factors for locally advanced esophageal cancer treated with neoadjuvant chemotherapy.

Materials and Methods

Study subject

Clinical data of patients with locally advanced esophageal carcinoma who underwent neoadjuvant chemotherapy at Sun Yat-sen Cancer Center between June 2007 and June 2011 were retrospectively analyzed. The screening criteria were as follows: (1) patients were clinically diagnosed with esophageal cancer or gastroesophageal junction tumors by gastroscopic biopsy; (2) patients presented with tumor infiltration into the esophageal adventitia layer and invasion into the mediastinum (≥T3), or suspected local lymph mode metastasis and unresectable tumors as evaluated by imaging methods; (3) patients underwent 2 to 3 cycles of neoadjuvant chemotherapy combined with surgery; (4) all patients had appreciable postoperative pathologic specimen before and after chemotherapy. Neoadjuvant chemotherapy consisted of docetaxel (75 mg/m^2) and nedaplatin (80 mg/m^2) repeated every 21 days. Treatment efficacy and performance status were evaluated 3 to 4 weeks after chemotherapy. Patients with progression-free tumors and a performance status score ≤2 underwent radical surgical resection. Exclusion criteria were as follows: 1) patients had progressive esophageal carcinoma after chemotherapy; 2) patients had a performance status score >2.

Efficacy evaluation

Resected tumor foci were evaluated by using the TRG criteria reported by Wu *et al.*[8] and recommended by NCCN guidelines for esophageal carcinoma (2011 edition)[12]: G0, no residual cancer cells; G1, 1% to 50% residual cancer cells; G2, >50% residual cancer cells.

Statistical analysis

SPSS 16.0 software was used for statistical analysis. Chi-square test and Fisher's exact test were used to determine the correlation between clinicopathologic factors and TRG. Grading data were analyzed by Spearman rank correlation. Survival, which was considered the time from diagnosis to death or final follow-up, was calculated by using the Kaplan-Meier method, and survival curves were compared with the log-rank test. Multivariate analysis with Cox regression was used to determine the prognostic factors. $P < 0.05$ was considered significant.

Results

Patient information

Among 122 patients with locally advanced esophageal carcinoma who underwent neoadjuvant chemotherapy between June 2007 and June 2011, 52 met the inclusion criteria, including 43(82.7%) men and 9(17.3%) women ranging in age from 39 to 73 years (median, 55 years). There were 43 cases (82.7%) of esophageal squamous cell cancer and 9 cases (17.3%) of esophageal adenocarcinoma. All patients completed 2 cycles of chemotherapy. All specimens were pathologically proved negative at the incision edge (R0 resection).

Efficacy evaluation

Spearman analysis showed that TRG was significantly correlated with postoperative pathologic T category (P = 0.006) and N category (P < 0.001), but was not correlated with sex, age, histological subtype, or tumor site (Table 1).

Survival analysis

The median follow-up for all 52 patients with locally advanced esophageal cancer was 21.6 months, and the median survival time was 33 months. Eighteen patients died. The survival rate was 71% in the first year and 44% in the second year. Survival was better in patients with low TRG than in those with high TRG (χ^2 = 6.405, P = 0.041, log-rank test) (Figure 1). Univariate analysis revealed that histological subtype (P = 0.003), tumor site (P = 0.044), postoperative pathologic T category (P = 0.026), pathologic N category (P < 0.001), and TRG (P = 0.041) were prognostic factors (Figures 2–5). Multivariate analysis with Cox regression suggested that pathologic N category was an independent prognostic parameter (Table 2).

Discussion

There has been no standard treatment for locally advanced esophageal carcinoma. Preoperative neoadjuvant chemotherapy and chemoradiotherapy are being explored as treatment strategies for this type of cancer. However, the value of neoadjuvant chemotherapy or chemoradiotherapy in treating esophageal cancer remains elusive[13]. Some investigations indicated that neoadjuvant concurrent chemoradiotherapy yielded higher response rate than neoadjuvant chemotherapy. However, concurrent chemoradiotherapy produced more adverse events, elevated surgical risk, prolonged treatment duration, and increased financial burden compared with chemotherapy alone[14,15]. The value of neoadjuvant chemotherapy in treating esophageal

Table 1. Correlation between tumor regression grade (TRG) and clinicopathologic characteristics of 52 patients with locally advanced esophageal cancer

Characteristic	Total [cases (%)]	TRG			r	P
		G0 (n = 9)	G1 (n = 20)	G2 (n = 23)		
Gender					0.066	0.893
Male	43 (82.7)	7	17	19		
Famale	9 (17.3)	2	3	4		
Age (years)					0.109	0.442
< 55	29 (55.8)	5	13	11		
⩾55	23 (44.2)	4	7	12		
Tumor type					0.241	0.202
Squamous cell carcinoma	43 (82.7)	9	17	17		
Adenocarcinoma	9 (17.3)	0	3	6		
Tumor location					0.169	0.681
Upper esophagus	6 (11.5)	1	2	3		
Middle esophagus	30 (57.7)	7	12	11		
Lower esophagus	9 (17.3)	1	4	4		
Gastroesophageal junction	7 (13.5)	0	2	5		
YpT					0.374	0.006
T0	6 (11.5)	5	1	0		
T1	5 (9.6)	1	2	2		
T2	11 (21.2)	2	3	6		
T3	30 (57.7)	1	14	15		
YpN					0.518	<0.001
N0	21 (40.4)	9	7	5		
N1	15 (28.8)	0	9	6		
N2	8 (15.4)	0	2	6		
N3	8 (15.4)	0	2	6		

YpT, pathologic T stage after neoadjuvant chemotherapy; YpN, pathologic N stage after neoadjuvant chemotherapy.

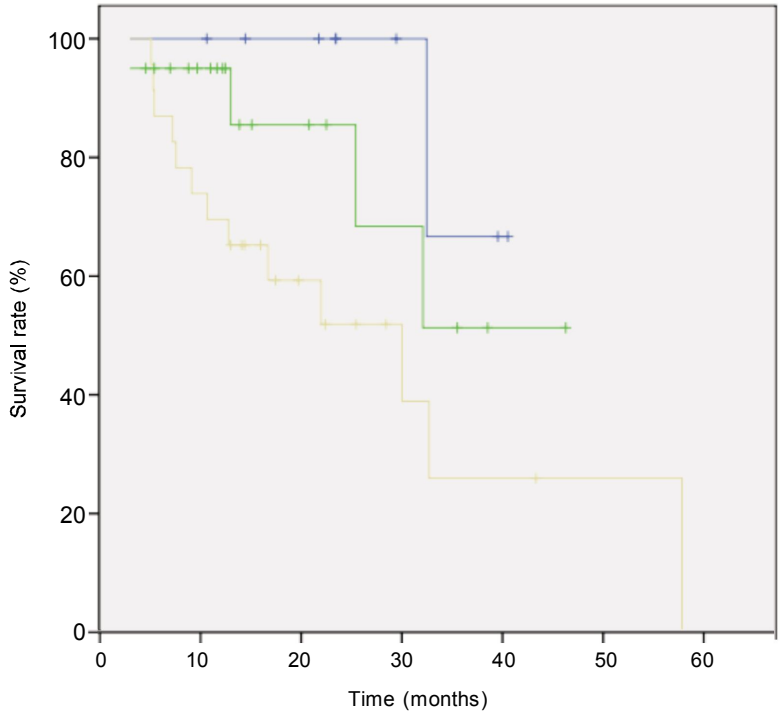

Figure 1. Kaplan-Meier overall survival curves for patients with locally advanced esophageal carcinoma of different tumor regression grades (TRG). The difference between groups (G0, *n* = 9; G1, *n* = 20; G3, *n* = 23) was compared with the log-rank test. The survival rate of the was significantly higher in G0 group than in other groups (*P* = 0.041).

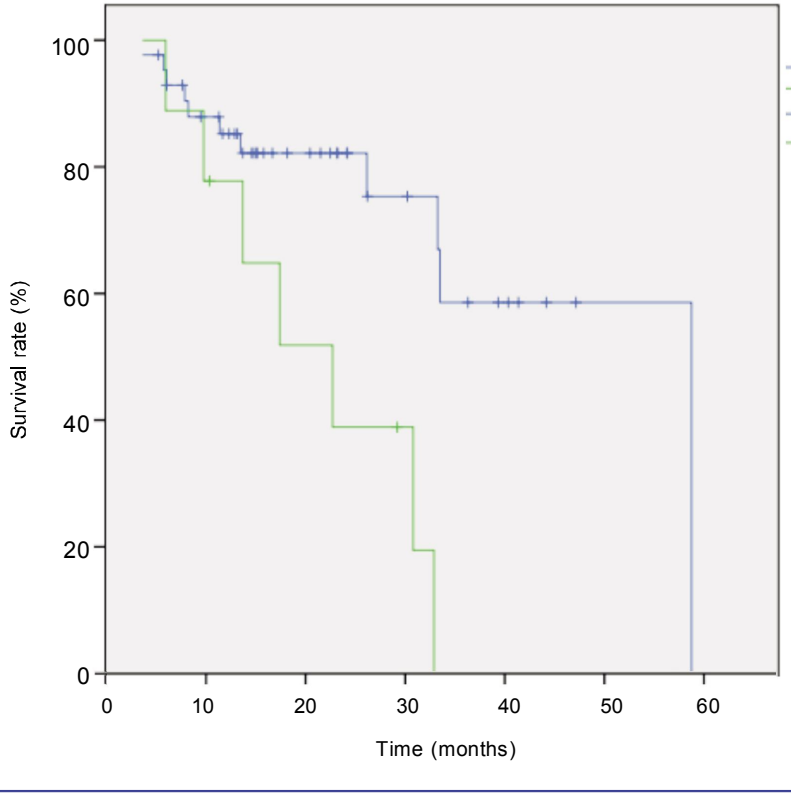

Figure 2. Kaplan-Meier overall survival curves for patients with locally advanced esophageal carcinoma of different types. The difference between tumor types (squamous carcinoma, *n* = 43; adenocarcinoma, *n* = 9) was compared with the log-rank test. The survival rate was significantly higher in patients with squamous cell carcinoma than in those with adenocarcinoma (*P* = 0.003).

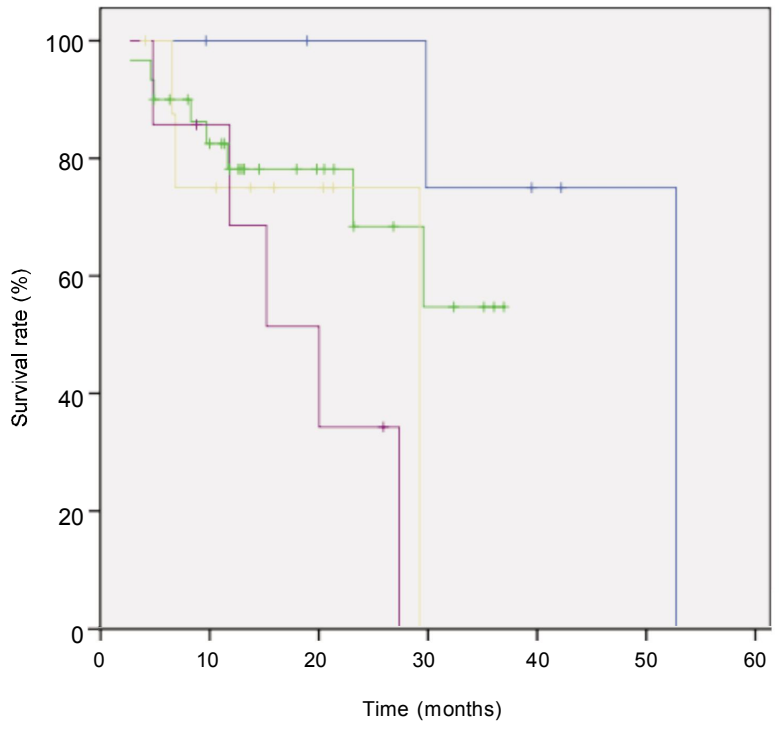

Figure 3. Kaplan-Meier overall survival curves for patients with locally advanced esophageal carcinoma at different locations. The difference between tumor locations (upper esophagus, n = 6; middle esophagus, n = 30; lower esophagus, n = 9; gastroesophageal junction, n = 7) was compared with the log-rank test. The survival rate was significantly higher in upper esophagus group than in other groups (P = 0.044).

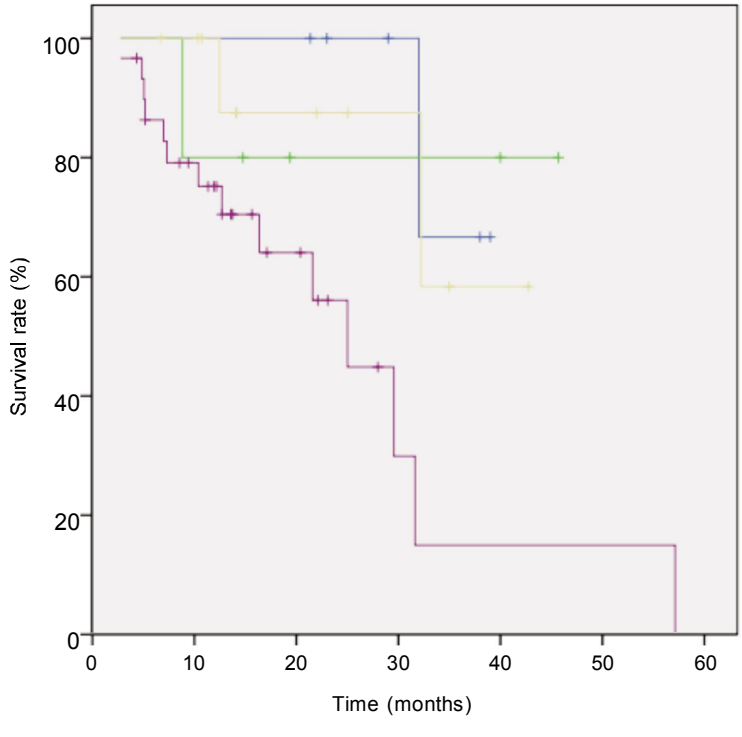

Figure 4. Kaplan-Meier overall survival curves for patients with locally advanced esophageal carcinoma of different pathologic T stage after neoadjuvant chemotherapy. The difference between groups (T0, n = 6; T1, n = 5; T2, n = 11; T3, n = 30) was compared with the log-rank test. The survival rate was significantly higher in T0 group than in other groups (P = 0.026).

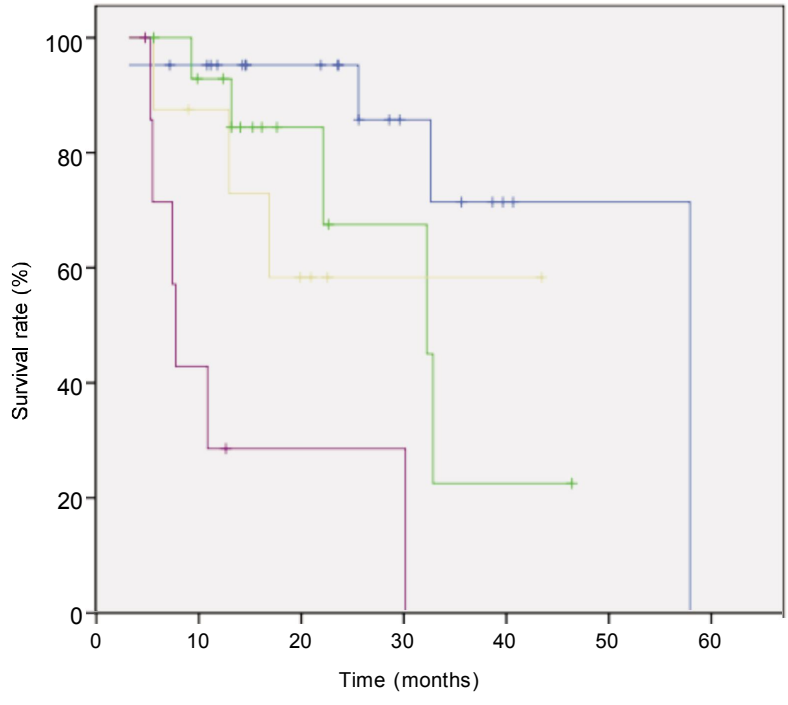

Figure 5. **Kaplan-Meier overall survival curves for patients with locally advanced esophageal carcinoma of different pathologic N stage after neoadjuvant chemotherapy.** The difference between groups (N0, n = 21; N1, n = 11; N2, n = 8; N3, n = 8) was compared with the log-rank test. The survival rate was significantly higher in N0 group than in other groups (P < 0.001).

carcinoma is under debate. Different and even opposing results have been obtained due to different treatment schemes and chemotherapy cycles[16]. However, neoadjuvant treatment has generally satisfactory outcomes. After neoadjuvant chemotherapy, potentially resectable cases of locally advanced esophageal cancer evolved into completely resectable cases. Furthermore, the R0 resection rate of significantly increased and postoperative quality of life was enhanced[17]. Previously used chemotherapy for esophageal cancer was primarily 5-fluorouracil (5-FU) combined with cisplatin continuous infusion. However, chemotherapy agents, such as taxol, docetaxel, oxaliplatin, nedaplatin, have been widely used in clinical settings. Thus, whether neoadjuvant chemotherapy and chemoradiotherapy can bring survival benefits remains unanswered[18-20]. Previous phase III CROSS [21] and GALGB9781 [22] trials suggested that neoadjuvant chemoradiotherapy increased overall survival compared to surgery alone. Phase III FFCD9901[23] and FFCD9102 [24] clinical trials failed to confirm that neoadjuvant chemoradiotherapy improved overall survival. In contrast, results from the MRCOEO2[25] and FNLCCACCORD07-FFCD9703 [26] clinical trials and MAGIC experiment[27] showed that neoadjuvant chemotherapy plus surgery enhanced survival rate compared to surgery alone. The RTOG8911 clinical trial [28] showed that the survival between neoadjuvant chemotherapy with surgery group and surgery alone group did not significantly differ. Sjoquist *et al.* [29] conducted a meta-analysis of esophageal cancer with neoadjuvant therapy incorporating 17 previous meta-analysis studies and 7 new investigations. Twelve studies compared neoadjuvant chemoradiotherapy and surgery alone (n = 1854); 9 trials compared neoadjuvant chemotherapy and surgery alone (n = 1981); 2 compared neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy (n = 181); and 1 performed pairwise comparison, including both neoadjuvant chemoradiotherapy and chemotherapy (n = 81). The results validated that neoadjuvant chemoradiotherapy and chemotherapy yielded greater survival benefits compared to surgery alone. However, these studies failed to confirm that neoadjuvant chemoradiotherapy afforded advantages over neoadjuvant chemotherapy. The divergent outcomes are ascribed to multiple factors, such as histological subtypes, chemotherapy schemes, chemotherapy cycles, tumor grade, and so on. The evaluation criterion of the efficacy of neoadjuvant therapy may be a possible factor.

Objective and accurate evaluation of clinical efficacy can provide guidance for treatment and is valuable for predicting prognosis and survival. Postoperative TRG is the golden standard for determining the clinical efficacy of neoadjuvant chemotherapy and chemoradiotherapy. At present, TRG is frequently adopted to assess the

Table 2. Univariate and multivariate survival analyses on 52 patients with locally advanced esophageal cancer

Variate	Total number	Number of deaths	Univariate analysis (*P*)	Multivariate analysis (*P*)
Gender			0.879	0.897
Male	43	16		
Female	9	2		
Age (years)			0.422	0.682
<55	29	10		
⩾55	23	8		
Tumor type			0.003	0.104
Squamous cell carcinoma	43	11		
Adenocarcinoma	9	7		
Tumor location			0.044	0.099
Upper Esophagus	6	2		
Middle Esophagus	30	8		
Lower Esophagus	9	3		
Gastroesophageal junction	7	5		
YpT			0.026	0.107
T0	6	1		
T1	5	1		
T2	11	2		
T3	30	14		
YpN			<0.001	<0.001
N0	21	4		
N1	15	5		
N2	8	3		
N3	8	6		
TRG			0.041	0.464
G0	9	1		
G1	20	4		
G2	23	13		

Footnotes as in Table 1.

efficacy of neoadjuvant therapy on esophageal carcinoma[30]. Mandard *et al.*[10] classified the percentage of residual cancer cells and the degree of lesion fibrosis into five grades. Chirieac *et al.*[9] divided the percentage of residual cancer cells into four grades (G0, 0%; G1, 1%–10%; G2, 11%–50%; and G3, >50%). Survival analysis revealed that patients in the G0 group had significantly longer survival compared with their counterparts in the G3 group, whereas the survival between the G1 and G2 groups did not differ. Wu *et al.*[8] categorized TRG into three grades based upon previous investigations (G0, 0%, G1, 1%–50%, and G2, >50%), which reflected prognosis and survival in a more object manner. Although current TRG evaluation criteria have not been applied, the 3-grade classification used by Wu *et al.*[8] has been widely recognized by pathologists. The 2011 NCCN guidelines for esophageal cancer recommended the TRG criterion for evaluating the efficacy of neoadjuvant therapy on esophageal cancer.

A recent report indicated that an R0 resection rate of 89% was achieved for esophageal cancer after neoadjuvant chemotherapy. Survival analysis revealed that positive lesion incision edge was an indicator of poor prognosis [31]. Another multi-center clinical trial (SAKK75/02) found that the R0 resection rate of the patients with locally advanced esophageal carcinoma was 93% following neoadjuvant chemoradiotherapy[32]. In our study, we retrospectively analyzed 52 cases of stage III esophageal cancer treated with neoadjuvant TP scheme (docetaxel and nedaplatin) preoperatively. The R0 resection rate was 100%. Collectively, our results and results from other studies suggest that both neoadjuvant chemotherapy and chemoradiotherapy can enhance the rate of radical operation, increase R0 resection rate, and lower the incidence of recurrent esophageal tumors.

This study showed that 9 (17.3%) patients had complete histopathologic response. Correlation analysis revealed that histopathologic response was highly correlated with pathologic T category ($P = 0.006$) and N

category ($P < 0.001$), which were in line with previous studies. Langer *et al.*[33] analyzed TRG in 92 cases of esophageal cancer treated with neoadjuvant chemotherapy. The results indicated that TRG was significantly correlated with incision edge ($P = 0.016$), postoperative pathologic T category ($P < 0.001$), and N category ($P = 0.001$). Some studies showed that complete pathologic response was achieved in >20% of cases after neoadjuvant chemoradiotherapy [34,35], which was higher than in the current study. This is possibly because concurrent chemoradiotherapy increased TRG.

Survival analysis in our study indicated that the survival among the G0, G1, and G2 groups significantly differed ($P = 0.041$), suggesting that TRG has a good value for predicting prognosis of esophageal cancer patients after neoadjuvant chemotherapy. Indeed, the patients who showed complete pathologic response (G0) had significantly prolonged survival. In univariate analysis, histological subtype, tumor site, pathologic T category, and N category were prognostic parameters. Histological subtype has been widely recognized as a prognostic factor for esophageal carcinoma. Previous studies noted that the prognosis of squamous cell cancer and adenocarcinoma significantly differed[36]. In the 7th edition of the American Joint Committee on Cancer (AJCC) manual, separate grading systems were applied for these two different histological subtypes. In addition, Gebski *et al.*[37] performed a meta-analysis study and found that adenocarcinoma patients were more likely to gain survival benefits from neoadjuvant therapy compared to squamous cell cancer subjects. Our results were similar. Previous investigations found that the effect of tumor site on survival was limited to early-stage squamous cell cancer patients (stage IB–IIB). Therefore, tumor site should be considered for this population. In our retrospective study, we observed that tumor site is a prognostic parameter, probably due to the influence of gastroesophageal cancer. However, histological subtype exerted a higher effect on survival compared to tumor site.

Multivariate analysis with Cox regression revealed that postoperative pathologic N category was an independent prognostic parameter. Based on previous studies, participants were classified into two groups according to the percentage of residual cancer cells (<10% versus ⩾10%). Survival curves indicated that the group with fewer residual cancer cells (<10%) have better survival ($P < 0.004$). Cox regression model analysis revealed that postoperative residual cancer cells ($P < 0.028$) and postoperative lymph node (YpN) status ($P < 0.036$) were prognostic factors but pathologic T category was not ($P = 0.900$)[38], suggesting that TRG better reflects the changes in tumor lesions following neoadjuvant treatment compared to pathologic T category. In our study, multivariate analysis indicated that TRG was not an independent prognostic factor for esophageal cancer patients, possibly due to limited sample size of patients with G0 in this cohort analysis. Thus, the survival status of this population was not objectively illustrated. The prognostic significance of pathologic T category upon survival indicate that neoadjuvant chemotherapy controlled primary lesions well. Local lymph node status became a more vital influencing factor for survival. Hence, the patients diagnosed with lymph node metastasis were required to undergo adjuvant chemotherapy postoperatively to reduce distant metastasis.

Conclusions

After neoadjuvant chemotherapy, TRG is highly correlated with pathologic T category and N category. Furthermore, TRG is a prognostic factor. Similarly, pathologic N category is also an independent prognostic factor for esophageal cancer patients treated with neoadjuvant chemotherapy. TRG criteria can be used to predict long-term survival of esophageal cancer patients. Hence, the TRG evaluation system has significant potential for assessing the clinical efficacy of neoadjuvant chemotherapy on esophageal carcinoma.

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