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DISEASES OF THE ESOPHAGUS

Original article

Effects of neoadjuvant chemotherapy on primary tumor and lymph node metastasis in esophageal squamous cell carcinoma: additive association with prognosis

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SUMMARY. **Neoadjuvant chemotherapy (NACT) is widely used to treat esophageal squamous cell carcinoma with lymph node metastasis (ESCC). However, NACT frequently has differential effects on primary tumor (PT) and lymph node metastasis (LNM). The clinical significance of this phenomenon remains unclear. Reduction in tumor size of PT and LNM was evaluated separately in 47 node-positive ESCC patients undergoing NACT, followed by surgical resection. We analyzed the prognostic significance and various clinicopathological parameters. NACT resulted in an average reduction rate of 45.5% for PT and 36.6% for LNM; the correlation between these rates was weak but significant ($r^2 = 0.122$, $P = 0.016$). The reduction rates in both PT and LNM were significant prognostic factors, with the maximal significance with cut-off at 30% size reduction for PT (3-year survival, 47.3 *vs.* 8.3%, $P = 0.0004$) and 20% for LNM (51.3 *vs.* 7.1%, $P = 0.0013$). When these cut-off values were used to define NACT response, 28 patients (59%) were deemed responders for both PT and LNM, while 7 (15%) were nonresponders for both, and the response was inconsistent in 12 patients (26%). Only both PT/LNM responders showed good survival rates, with the remaining categories showing poor survival (3-year survival 60.5 *vs.* 5.3% $P < 0.0001$). Multivariate analysis identified neither the PT nor the LNM response alone as an independent prognostic factor; however the combined PT/LNM response was identified as an independent prognostic factor (hazard ratio [HR] 2.861, $P = 0.0255$) in addition to the number of histological lymph node metastases (HR 2.551, $P = 0.0328$). The response to NACT in LNM and PT correlates closely with postoperative survival. A good response in both enhances the postoperative prognosis.**

KEY WORDS: **esophageal cancer, lymph node metastasis, neoadjuvant chemotherapy, prognostic factor.**

INTRODUCTION

Surgery is generally regarded as the standard treatment for squamous cell carcinoma of the esophagus (ESCC). However, the prognosis of patients with ESCC after curative resection remains unsatisfactory, with more than 50% of patients developing tumor recurrence in distant and/or locoregional sites. Neoadjuvant chemoradiotherapy may improve the local control and short-term survival of patients with locally advanced ESCC.[1] On the other hand, neoadjuvant chemotherapy (NACT) may further improve long-term survival, probably by eradicating systemic micrometastasis.[2–4] Cisplatin-based NACT is commonly used preoperatively in patients with ESCC.[5–7] In our department, we use two cycles of a cocktail of cisplatin, adriamycin, and 5-fluorouracil (5-FU) (FAP), which has resulted in high response rates and prolonged postoperative survival.[8,9] Since the benefits of adjuvant chemotherapy were observed only in node-positive ESCC patients,[10] we generally use FAP-based NACT in ESCC patients with regional lymph node metastasis.

Evaluation of the response to NACT in ESCC patients is important due to its predicted prognostic value and that only responders receive the benefits of NACT.[11] In general, the effect of NACT was evaluated by the size-reduction rate of the primary tumor (PT), while lymph node metastasis (LNM) had been

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ignored, since LNM was smaller and considered to be less important for survival than the PT. However, micrometastasis, the target of any NACT, is closely associated with presence of LNM,[4,12,13] and response to NACT is not always the same in PT and LNM. These findings suggest that the response of LNM to NACT may carry a different prognostic significance from that of PT. The present study was designed to evaluate the separately response of PT and LNM to NACT, and compare the response of each with postoperative survival, and then combine the response of both the PT and LNM to produce a more comprehensive system for NACT-response evaluation. We also discuss the clinical applications and indications of this multimodal therapy.

MATERIALS AND METHODS

Patients

From October 1997 to September 2004, 381 ESCC patients underwent esophagectomy in our department. Of these, 140 received preoperative treatment: 107 with NACT (FAP: 104 and cisplatin plus 5-Fu: 3), 29 with chemoradiotherapy, and 4 with endoscopic mucosal resection. For the remaining 241 patients who did not receive preoperative treatment, 38 and 12 patients received adjuvant chemotherapy and postoperative chemoradiotherapy, respectively. Our strategy for the treatment of ESCC was as follows:[4,11] NACT was applied for cN1 or cM1lym with any cT stage, chemoradiotherapy for T4N0, and surgery without preoperative treatment for T1, T2, or T3N0. High-risk patients, including those aged over 75 years, underwent surgery, followed by postoperative chemotherapy if indicated. Any M1 other than metastasis in the distant node was not indicated for surgery.

In addition to the above criteria, patients were scheduled for NACT if the Eastern Cooperative Oncology Group performance status was 0 to 1, and had normal functions of the bone marrow, kidney, and liver. The treatment regimen of FAP chemotherapy included cisplatin at a dose of 70 mg/m^2 and doxorubicin hydrochloride (adriamycin) at a dose of 35 mg/m^2, administered by slow-drip infusion on day 1 and 5-FU administered at a dose of 1000 mg/body by continuous infusion on days 1 through 7. Patients underwent two rounds of chemotherapy, separated by a 4-week interval.

Patients underwent surgery on average 3 weeks after the completion of NACT. Esophagectomy via right thoracotomy, followed by reconstruction using gastric conduit, together with two- or three-field lymphadenectomy, was performed as reported previously.[14,15] After surgery, the patients were surveyed every 3 months by physical examination and measurement of serum tumor markers, every 6 months by computed tomography (CT) scan and abdominal ultrasonography, and every year by fiberscopy until tumor recurrence was evident. Bone scintigraphy was also performed if the patient complained of persistent and localized bone pain.

Evaluation of effect of NACT by CT in PT and LNM

Patients with NACT underwent serial preoperative CT. Enhanced CT scanning with 5-mm slices was repeated within 2 weeks before starting the first cycle of chemotherapy and 14 $\pm$ 5 days after the completion of each cycle of chemotherapy.

The CT slice that included the largest tumor area was digitized using a film scanner (ES-2000, SEIKO EPSON, Nagano, Japan). The tumor area was demarcated and measured using Aquarius Workstation Version 3.3 (TeraRecon, CA, USA). The areas of PT and LNM, defined as more than 1 cm in diameter, were measured separately. The reduction rate (RR) was calculated as follows: (tumor area before treatment – area after NACT)/tumor area before treatment. A single measurement of the longest diameter based on RECIST criteria was not used here, since primary esophageal cancers are frequently oval and/or irregularly shaped. Fiberscopic examination was performed for all patients after NACT and biopsy specimen was taken when complete remission was suspected.

Patients' enrollment

Sixty out of 107 patients with NACT were excluded from this study for various reasons: three patients received a chemotherapy protocol not using FAP, six patients died of other causes (one of postoperative complication, three of other malignant tumors, two of other nonmalignant diseases), three patients received inadequate postoperative follow-up, and 48 patients had inadequate CT imaging. Since our study was retrospective, it was based on various conditions of CT examination. We excluded patients with inadequate CT scans as follows: (i) not performed, before or after NACT; (ii) performed out of the indicated period; (iii) performed with 10-mm slice; or (iv) performed without contrast enhancement.

Patient characteristics are shown in Table 1. Most patients were men, with a median age of 60.7 years (range, 50–75). The UICC-TNM classification[16] before treatment showed 20 and 23 patients to be cT3 and cT4, respectively, 21 and 26 patients to be cN1 and cM1lym, respectively, and 20 and 26 patients to be stage III and IV, respectively. There were no hematogenic or disseminated metastases in this series. The median follow-up period for the final 47 patients was 56.9 months (range 27–111).

Among the 47 patients enrolled in this study, 43 patients received two cycles of FAP, while 4 patients

Table 1 Background of ESCC patients undergone neoadjuvant chemotherapy

	Number of patients
Sex	
Male/female	40/7
Age	
Average (range)	60.7 (50–75)
Tumor location†	
Upper/middle/lower	3/24/20
Histology‡	
Poor/mod/well	8/30/9
Depth of invasion†	
cT2/cT3/cT4	4/20/23
Lymph node metastasis†	
cN0/cN1/cM1lym	0/21/26
Pathological depth of invasion	
pT0/pT1/pT2/pT3/pT4	1/6/5/26/9
Number of pathological lymph node metastasis	
0/1–3/4–7/8–	7/22/4/14

†According to TNM classification; ‡Poorly, moderately and well-differentiated squamous cell carcinoma. ESCC, esophageal squamous cell carcinoma.

received only the first cycle. Two of these patients refused the second cycle because of severe adverse effects, and tumor size reduction was not observed in the other two patients. No patient died of chemotherapy-related causes during treatment. Eight patients received a 30% dose reduction for the second cycle due to grade-3 or higher toxicity in the first cycle, assessed by NCI-CTC criteria (six hematogenic and two gastrointestinal toxicities).

Persistent T4 at surgery was observed in 13 of the 47 patients. Curative resection was performed by combined resection of the diaphragm in four of these cases, the pericardium in three cases, the lung in two cases, and the bronchus in one patient; curative resection was abandoned in 3 of the 13 patients. Operative morbidity was 35%, representatively including 25% with pneumonia, 18% with recurrent nerve paralysis, and 5% with anastomotic leakage.

Statistical analysis and ethical issues

Data are expressed as mean ± standard deviation. Differences in continuous values, including tumor area and RR, were evaluated by the Student's *t*-test (Fig. 1). We evaluated correlations between the RR of PT and LNM by the linear regression model (Fig. 2). Disease-free survival rates were calculated by the Kaplan–Meier method and evaluated by the log-rank test (Figs. 3 and 4, Table 2). Cox's proportional hazard regression model with stepwise comparisons was used to analyze the independent prognostic factors (Table 3). The Fisher's exact probability test was used to compare discrete variables (Table 4). These analyses were carried out using StatView J 5.0 software (Abacus Concepts, Berkeley, CA, USA). A P value less than 0.05 indicated statistical significance.

The study protocol was approved by the Human Ethics Review Committee of Osaka Medical Center for Cancer and Cardiovascular and a signed consent form was obtained from each subject.

RESULTS

The mean area of PT was 8.48 ± 3.43 cm^2 before NACT, and decreased to 4.20 ± 3.31 cm^2 after

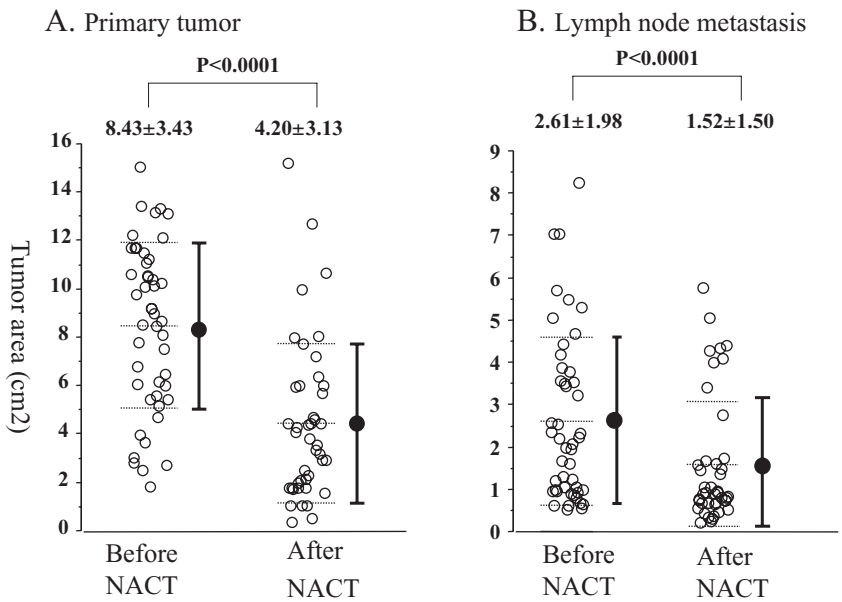

Fig. 1 Changes in size of primary tumor and lymph node metastasis after neoadjuvant chemotherapy (NACT). Open circles indicate the area of each tumor, together with the mean (closed circles) and standard deviation (bars). The mean area of both primary tumor and lymph node metastasis has significantly decreased after NACT from 8.48 ± 3.43 cm^2 to 4.20 ± 3.31 cm^2 and from 2.6 ± 1.98 cm^2 to 1.52 ± 1.50 cm^2, respectively (both $P < 0.0001$).

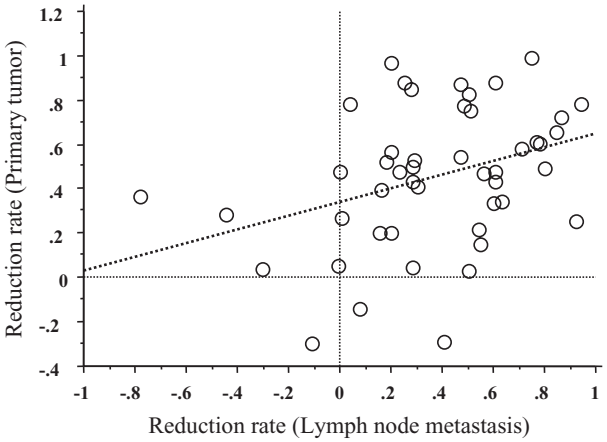

Fig. 2 Relationship between reduction rates of PT and LNM. PT and LNM size reduction rate was plotted for each patient. A weak but statistically significant correlation was identified by the linear regression model ($Y = 0.342 + 0.308 * X$, $R^2 = 0.122$, $P = 0.016$). LNM, lymph node metastasis; PT, primary tumor.

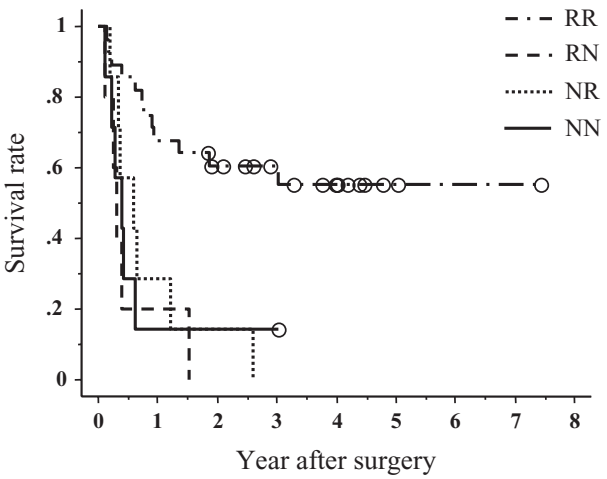

Fig. 4 Survival curves of ESCC patients according to the combined evaluation of NACT responses in PT and LNM. Disease-free survival curves were plotted separately, classified by combined evaluation of NACT response in PT and LNM. RR: responders in both PT and LNM ($n = 28$), RN: responder in PT and nonresponder in LNM ($n = 5$), NR: nonresponder in PT and responder in LNM ($n = 7$), and NN: nonresponders in both ($n = 7$). A significant difference by log-rank test was observed between RR and the others ($P < 0.0001$). ESCC, esophageal squamous cell carcinoma; LNM, lymph node metastasis; NACT, neoadjuvant chemotherapy; PT, primary tumor.

NACT. The same values for LNM were $2.61 \pm 1.98\ cm^2$ and $1.52 \pm 1.50\ cm^2$, respectively (Fig. 1). Although the tumor sizes of PT and LNM were significantly different ($P < 0.0001$), the reduction rates were not significantly different between PT and LNM (45.5 and 36.6%, $P = 0.205$). Analysis of the reduction rates of PT and LNM in each patient showed only a weak correlation by linear regression model ($r^2 = 0.122$, $P = 0.016$, Fig. 2). We next examined the correlation between NACT response and postoperative survival. To find the optimal cut-off line for each target lesion, which would provide the maximal and most significant differences in postoperative survival between NACT responders and nonresponders, we compared the disease-free survival rates at the 10% stepwise cut-off line (Table 2). With respect to PT, each cut-off line from 10 to 50% showed a significant survival difference between responders and nonresponders, with the most significant difference obtained at the 30% cut-off line (3-year survival; responders 51.3%, nonresponders 7.1%, $P = 0.0013$). On the other hand, the 20% cut-off line provided the most significant difference for LNM (3-year survival; responders 47.3%, nonresponders 8.3%, $P = 0.0004$) (Fig. 3). Using these cut-off lines, i.e., 30% for PT and 20% for LNM, to classify the responders and nonresponders for NACT, indicated 28 patients (59%) as responders for both PT and

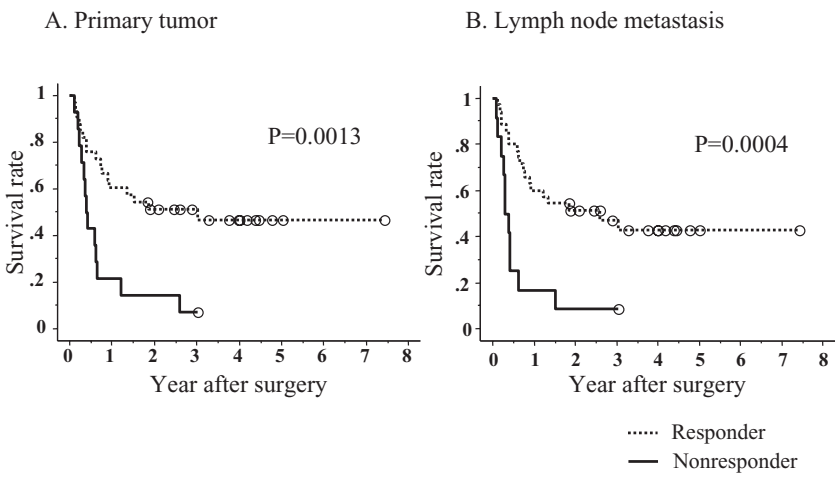

Fig. 3 Survival curves of ESCC patients according to PT- and LNM-NACT responses. Disease-free survival curves were plotted by the Kaplan–Meier method, with *P*-values calculated by the log-rank test. Patients were separated into responders and nonresponders by the optimal cut-off lines of size reduction rate (30% for PT and 20% for LNM). ESCC, esophageal squamous cell carcinoma; LNM, lymph node metastasis; NACT, neoadjuvant chemotherapy; PT, primary tumor.

Table 2 Effect of neoadjuvant chemotherapy on postoperative disease free survival, based on stepwise cut-off line

	Cut-off line of reduction rate				
	10%	20%	30%	40%	50%
Primary tumor					
Number of patients					
Responder	40	39	33	30	21
Nonresponder	7	8	14	17	26
3-year disease-free survival rate (%)					
Responder	44.0	46.0	51.3	53.3	57.1
Nonresponder	0.0	0.0	7.1	11.8	23.1
P-value	0.0016	0.0067	0.0013	0.0059	0.0301
Lymph node metastasis					
Number of patients					
Responder	38	35	25	24	20
Nonresponder	9	12	22	23	27
3-year disease-free survival rate					
Responder	43.6	47.3	39.3	36.7	38.9
Nonresponder	11.1	8.3	36.4	39.1	37.0
P-value	0.0316	0.0004	0.6191	0.6347	0.3157

LNM (R/R group), five patients (11%) as responders for PT but nonresponders for LNM (R/N group), seven patients (15%) as nonresponders for PT but responders for LNM (N/R group), and seven patients (15%) as nonresponders for both PT and LNM (N/N group). Next, we examined the postoperative survival curve among these four groups. Only the R/R group showed good survival, while the remaining three groups showed similarly poor survival, with the difference between R/R and the remainders significant (3-year survival; R/R 60.5%, the others 5.3%, $P < 0.0001$) (Fig. 4).

Table 3 Preoperative prognostic factors for postoperative survival by Cox proportional hazard model

	Univariate analysis		Multivariate analysis			
	HR	*P*-value	HR	*P*-value	HR	*P*-value
Sex†						
Male/female	1.494	0.4157	NI		NI	
Depth of invasion						
cT2, 3/cT4	1.211	0.6014	NI		NI	
Lymph node metastasis						
cN1/cM1lym	1.321	0.4546	NI		NI	
Pathological depth of invasion						
pT2, T3/pT4	4.525	0.0005	2.513	0.1491	1.508	0.4122
Number of LNM						
<4/≥4	4.464	<0.0001	2.674	0.0442	2.551	0.0328
Effect of NACT in PT						
Responder/nonresponder	3.182	0.0023	1.044	0.9462	NI	
Effect of NACT in LNM						
Responder/nonresponder	3.655	0.0009	1.815	0.2397	NI	
Combined evaluation‡						
RR/RN + NR + NN	4.853	<0.0001	NI		2.861	0.0255

†Classification and number of cases referring to Table 1; ‡RR, both responder, RN and NR either responder, NN both nonresponder, classification of responder and nonresponder referring to Table 2 and the text.
HR, hazard ratio; LNM, lymph node metastasis; NACT, neoadjuvant chemotherapy; NI, not included; PT, primary tumor.

Table 4 Characteristic of each responder and nonresponder in the primary tumor and lymph node metastasis

	Primary tumor			Lymph node metastasis		
	Responder	Nonresponder	*P*-value	Responder	Nonresponder	*P*-value
Pathological depth of invasion						
pT2,3/pT4	32/1	6/8	<0.0001	30/5	8/4	0.2050
The number of LNM						
<4/>4	24/9	5/9	0.0241	27/8	2/10	0.0004

LNM, lymph node metastasis.

We also investigated the prognostic significance of various clinicopathological factors in ESCC patients treated by NACT and surgery. Prior to NACT, no parameters showed prognostic significance by univariate analysis, including age, sex, tumor size, depth of invasion, and regional/distant LNM (Table 3). After NACT, the separate responses in PT and LNM were significant prognostic factors (hazard ratio [HR] 3.182 and $P = 0.0023$, and HR 3.655 and $P = 0.0009$), but the combined response in PT and LNM (R/R and the others) was the strongest significant factor (HR = 4.853 and $P < 0.0001$). After surgery, pathological depth of tumor invasion and the number of pathological LNM was prognostically significant by univariate analysis (HR = 4.525, $P = 0.0005$, HR = 4.464, $P < 0.0001$ and HR = 3.257, $P = 0.0047$, respectively, Table 3). Multivariate analysis of the perioperative clinicopathological factors identified only the combined response in PT and LNM, as well as the number of pathological LNM as independent prognostic factors (Table 3). The separate responses of PT and LNM to NACT were not independent prognostic factors. Next, we investigated the influence of PT and LNM responses on various pathological factors in surgical specimens. As shown in Table 4, the PT response was significantly associated with pathological tumor depth and number of LNM. However, the LNM response was significantly associated only with number of LNM, which tended to be more closely related to the LNM response than the PT response ($P = 0.0004$ *vs.* $P = 0.0241$).

DISCUSSION

This study revealed that evaluating the effects of NACT on PT and LNM is a useful predictor of prognosis. In addition, there was a significant additive effect on prognosis when examining the combined responses of PT and LNM.

A simple speculation for this additive effect is that estimating two lesions is less influenced by measurement error than doing each separately. However, it is more likely that a biological difference in chemosensitivity exists between PT and LNM within each patient. The mean tumor reduction rate was not different between PT and LNM, though the PT area was larger than that of the LNM. However, the reduction rates of PT and LNM only weakly correlated, and these evaluations were frequently inconsistent. A similar discrepancy in responses to preoperative treatment in PT and LNM was observed in patients with colorectal cancers.[17,18] Several studies also revealed differences in gene expression in metastatic tumor compared with primary lesion with respect to tumor angiogenesis, chemokines, and cell–cell or cell–extracellular matrix interactions, among others.[19–21] On the other hand, sensitivity to chemotherapy was reported to be correlated with various gene expression, including components of apoptotic and DNA-repair pathways.[22,23] Although the genes implicated in metastasis and chemosensitivity are not identical, such comprehensive gene expression analyses should reveal common pathways involved in both metastasis and chemosensitivity.

It was of interest that the NACT responses in PT and LNM associated differently with pathological factors in the surgical specimen; the response in PT was associated with both depth of tumor invasion and number of LNM, while that in LNM was significantly associated only with number of metastases. In addition, the number of LNM tended to be more strongly associated with LNM response than with PT response. Since the major target of NACT is systemic micrometastasis, which is itself associated with number of LNM,[4,24] precise evaluation of NACT responses in LNM would be more clinically important than of those in PT. We have introduced a FDG-PET (^{18}F-fluorodeoxyglucose-positron emission tomography) approach to address this assertion. The results of PET scanning correlated more closely with viable tumor volume and were less affected than CT by the interstitial reaction, including inflammation, edema, and fibrosis.[25] PET may also reduce the false-positive number of LNM common on CT scans. In general, lymph nodes over 1 cm in diameter are regarded as positive, which accounts for 81% of positive predictive value in the literature.[26] In this study, seven patients were node-negative by pathological examination of surgical specimens. We could not distinguish whether these lymph nodes were false-positive or ablated by NACT. We consider NACT useful for node-positive patients; therefore, PET would provide a valuable means of selecting such patients.

In this study, we used cut-off lines calculated from survival analysis to separate NACT responders and nonresponders for PT (reduction rate 30%) and LNM (20%). In general, a 50% reduction in two-dimensional area or 30% in one-dimensional area were used as the cut-off lines to evaluate responses to chemotherapy.[27] Alternatively, time to progression or progression-free survival could be used to evaluate some therapies aimed at tumor dormancy. The true purpose of NACT, to eradicate systemic micrometastases, is not measurable. However, it can be estimated by the size reduction of visible tumor, which is eventually removed by surgery. Only tumor recurrence after curative resection properly reflects the presence of systemic micrometastasis. The association between the degree of visible tumor size reduction and the probability of micrometastasis eradication remains unknown. Our cut-off line is thus still tentative, and further, large-cohort studies are needed to properly address this important issue.

Precise evaluation of NACT is necessary to construct a systematic strategy for ESCC. For example, nonresponders should be indicated for second-line chemotherapy, since not only CDDP but also taxan may be effective for ESCC.[7] The responders might receive further benefit from postoperative chemotherapy, since NACT is the most reliable in vivo chemosensitivity test. Recent successful results in clinical trial have extended the indications of NACT.[2,3,28] Personalized treatment following NACT based on the individual's response to NACT is the next important aspect to this work. Finally, this study provides a novel insight on NACT evaluation, i.e., combined evaluation of PT and LNM.

CONCLUSION

Response to NACT in ESCC patients often differs in PT and LNM, and each serves as a prognostic factor in node-positive ESCC. Therefore, combined evaluation of NACT on PT and LNM is the most significant prognostic factor, followed by the number of pathological LNM. Although each metastatic lymph node is generally removed easily by surgery and is not life threatening, clinicians should give more attention to subtle changes in LNM size during NACT. The success of recent clinical trials of NACT in esophageal cancers increases the importance of evaluating NACT responses in the future.

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