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Early response to neoadjuvant chemotherapy in advanced esophageal cancer evaluated by computed tomography predicts the utility of a second cycle of chemotherapy

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Abstract. Multi-course neoadjuvant chemotherapy (NACT) followed by surgery is a promising treatment for advanced esophageal cancer. However, non-responders may continue to receive ineffective treatment, since there are no definitive criteria for early discontinuation of NACT. In this study, we analyzed 103 advanced esophageal cancer patients treated with 2 cycles of NACT followed by surgery. Patients with >20% decrease in the size of the primary tumor as evaluated by computed tomography (CT) following the first cycle of chemotherapy, were defined as early responders and the remainder as early non-responders. Clinicopathological factors and prognosis were compared between the 2 groups. The reduction rate of the second cycle and progression-free survival (PFS) of early non-responders were significantly worse than those of early responders (p=0.0001 and 0.0375, respectively). In addition, pathological T stage, pathological assessment of tumor regression and number of metastatic lymph nodes were significantly unfavorable in early non-responders (p=0.023, 0.007 and 0.0041, respectively). Among the clinical factors that were available prior to administration of the second cycle, clinical T3 stage and early non-responder status were the only independent unfavorable factors (p=0.028 and 0.0062, respectively). Patients with both unfavorable factors had a significantly poorer PFS compared to the remaining patients and a PFS similar to those who had both factors but received only 1 cycle of NACT. In conclusion, the reduction rate of the primary tumor as evaluated by CT following the first cycle of NACT, may aid physicians in determining whether to administer a second cycle. In early non-responders bearing T3 tumors, NACT should be discontinued after the first cycle.

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Introduction

Surgery alone has not been effective in improving the prognosis of advanced esophageal cancer, despite recent advances in surgical techniques and perioperative management. Even following curative resection by esophagectomy with extended 3-field lymphadenectomy, cancer recurs in ~50% of patients (1). Thus, it is likely that systemic micrometastases are present outside the surgical field at the time of diagnosis. To improve the prognosis of advanced esophageal cancer, neoadjuvant chemotherapy (NACT), administered to eradicate systemic micrometastases, followed by surgical resection, is a promising treatment strategy. Recent studies have reported successful results with NACT (2,3). NACT has been shown to improve the prognosis of responders; however, non-responders suffer from the side effects in addition to losing valuable time seeking alternative treatments (2,4,5). As demonstrated by certain studies, the prognosis of non-responders may be worse than that of patients undergoing primarily surgical treatment (2,4,5). This is partly due to therapy-induced adverse events, selection of chemotherapy-resistant, more biologically aggressive tumors and delay of surgical treatment. Disease progression during ineffective chemotherapy may also be a factor contributing to the poor survival of non-responders. Therefore, prediction of the response to chemotherapy prior to treatment or early during the course of therapy, is critical. Despite intensive efforts to identify predictors of response prior to chemotherapy, there are currently no clear candidate predictors that may be applicable in daily practice (6-8).

In this study, we retrospectively attempted to identify criteria for discontinuing NACT after the first cycle, based on the response as evaluated by computed tomography (CT). Patients with advanced squamous cell carcinoma of the thoracic esophagus received 2 cycles of cisplatin-based chemotherapy as NACT and their response was evaluated by CT following the completion of each cycle.

Materials and methods

Patient eligibility. Between January, 2000 and December, 2008, a total of 988 patients with squamous cell carcinoma of the thoracic esophagus underwent esophagectomy at our hospitals. All patients underwent esophageal fiberscopy and CT scan for tumor staging, according to the 6th edition of the TNM classification (9). Patients satisfying the following criteria were enrolled in this study: i) no prior treatment for esophageal cancer; ii) ≤80 years of age; iii) a performance status (Eastern Cooperative Oncology Group) of 0 or 1; iv) tumor depth of T3 or less; v) no lymph node metastasis or curatively resectable lymph node metastases, including N1 or M1 LYM (cervical or celiac nodes); vi) 2 cycles of NACT comprising 5-fluorouracil (5-FU), adriamycin and cisplatin (FAP therapy) or only 1 cycle of NACT (FAP therapy) due to ineffectiveness; vii) primary tumors that were measurable by CT scan (>10 mm in diameter); viii) adequate organ function (leukocyte count at least in the lower limit of the normal range; platelet count of at least 100,000/mm^3; total bilirubin level of ≤2.0 mg/dl; aspartate and alanine aminotransferase levels ≤2.5 times the upper limit of the normal range; and serum creatinine ≤1.5 times the upper limit of the normal range); and ix) CT scans with 5-mm slices prior to NACT and following each cycle of chemotherapy.

The study protocol was approved by the Human Ethics Review Committee of Osaka Medical Center for Cancer and Cardiovascular Diseases, Kinki University and Osaka University Graduate School of Medicine. Written informed consent was obtained from each patient.

Neoadjuvant chemotherapy and evaluation of the response to chemotherapy. The regimen of FAP therapy was as follows: cisplatin at a dose of 70 mg/m^2 and adriamycin at a dose of 35 mg/m^2 were administered by a drip infusion on day 1. 5-FU was administered at a dose of 700 mg/m^2 by continuous infusion on days 1-7. Two cycles of chemotherapy were administered, separated by a 3-week interval (10,11). Patients underwent CT scans with 5-mm slices prior to chemotherapy and 2 weeks after the completion of each cycle. The chemotherapeutic response was evaluated by monitoring the area of the primary tumor. The largest area of the primary tumor was measured bidimensionally, using the greatest diameter and the greatest perpendicular distance. The reduction rate was calculated as: (tumor area prior to treatment - tumor area following treatment)/tumor area prior to treatment. Patients with >50% decrease in the size of the primary tumor after 2 cycles of chemotherapy were defined as responders. Patients with >20% decrease in the size of the primary tumor after the first cycle of chemotherapy were defined as early responders and the remaining patients as early non-responders.

Surgery and pathological findings. Patients were scheduled for surgery ~4 weeks after the last day of chemotherapy. Surgical therapy consisted of en bloc esophagectomy via right thoracotomy with 2- or 3-field lymphadenectomy and reconstruction using the stomach, jejunum or colon. Pathological T stage was determined according to the TNM classification (9). The pathological response of the primary tumor was defined according to the Japanese Classification of Esophageal Cancer, 10th edition (12) as: grade 3, complete disappearance of cancer cells; grade 2, >2/3 disappearance; grade 1, <2/3 disappearance; grade 0, no therapeutic effect.

Table I. Clinical characteristics of patients who received 2 cycles of neoadjuvant chemotherapy.

Variables	n
Gender	
Male	84
Female	19
Age (years)	64.4±8.5
Location	
Upper	7
Middle	55
Lower	41
cT[a]	
T1	2
T2	25
T3	76
cN[a]	
N0	3
N1	74
M1 LYM	26
cStage[a]	
IIA	3
IIB	14
III	60
IV	26

[a]cT, cN and cStage are as defined by the 6th edition of the TNM classification.

Statistical analysis. Statistical analyses were performed using Stat View 5.0J software (SAS Institute, Inc., Cary, NC, USA). Differences in continuous variables were evaluated using the Student's t-test. The association between two non-continuous parameters was evaluated using the Chi-square test. Univariate and multivariate survival analyses were performed using Cox's proportional hazards regression model. Survival was calculated by the Kaplan-Meier method and assessed by the log-rank test. A two-tailed $p<0.05$ was considered to indicate a statistically significant difference.

Results

Patient and tumor characteristics. A total of 103 patients with esophageal cancer received 2 cycles of NACT. The clinical characteristics of these patients are presented in Table I. The majority of the patients were clinically node-positive, since this was used as an indication for NACT. There were 17 patients with clinical stage II disease, 60 with stage III disease and 26 with stage IV disease. The median follow-up period was 25.7 months.

Chemotherapeutic response and reduction rate of the primary tumor in each cycle. Based on a 50% reduction rate as the

Table II. Baseline and pathological characteristics of early non-responders and early responders.

Variables	Early non-responders (n=21)	Early responders (n=82)	P-value
Baseline characteristics			
Gender			
Male	21	63	0.0011
Female	0	19	
Age (years)			
<70	17	60	0.51
≥70	4	22	
Location			
Upper	2	5	0.73
Middle	12	43	
Lower	7	34	
cT[a]			
T1-2	5	22	0.78
T3	16	60	
cN[a]			
N0-1	13	64	0.13
M1 LYM	8	18	
Reduction rate after the second cycle of chemotherapy	6.4±12.3%	23.4±22.0%	0.001
Pathological characteristics			
pT[a]			
T0-2	4	38	0.023
T3-4	17	44	
Pathological response of the primary tumor[b]			
Grade 0-1	19	57	0.009
Grade 2-3	0	22	
Number of metastatic lymph nodes	5.5±5.4	3.1±4.3	0.041

[a]cT, cN, and pT are as defined by the 6th edition of the TNM classification. [b]Pathological response of the primary tumor is as defined by the 10th edition of the Japanese Classification of Esophageal Cancer.

definition of response, 52 patients were classified as responders and the remaining 51 as non-responders. Responders had a significantly improved progression-free survival (PFS) compared to non-responders (p<0.0001, data not shown). The reduction rate after the first cycle was 37.2±18.7% and that after the second cycle was significantly lower (19.9±21.5%; p<0.0001) (Fig. 1).

Evaluation of early response using CT. To avoid repetition of ineffective therapy, we attempted to establish criteria for discontinuing NACT after the first cycle, based on the response as evaluated by CT. Of the 103 patients, 82 were early responders and 21 were early non-responders, using a 20% decrease in the primary tumor size after the first cycle as the definition of early response. The reduction rate of the second cycle was 23.4±22.0% in early responders and 6.4±12.3% in early non-responders (p=0.001). Fig. 2 shows the PFS curves according to early response status. The 3-year PFS rate of early responders and early non-responders was 53.2 and 22.2%, respectively, and early responders exhibited significantly higher survival rates, compared to early non-responders (p=0.0375). Table II lists the baseline and pathological characteristics of early responders vs. early non-responders. Females had a higher early response rate compared to males (p=0.0011). Early responders had a more favorable pathological T stage, pathological tumor response and number of metastatic lymph nodes, compared to early non-responders (p=0.023, 0.009 and 0.041, respectively).

Prognostic significance of early response. Among the clinical characteristics available prior to the initiation of the second cycle of chemotherapy, including gender (male/female), age (<70/>70 years), tumor location (upper/middle, lower esophagus), T stage (T1-2/T3), N stage (N0-1/M1 LYM) and early response status (early responder/early non-responder), T1-2 and early responder status were significantly correlated with higher PFS rates in a univariate analysis (p=0.031 and 0.032, respectively; Table III). A multivariate analysis using T stage and early responder status demonstrated that the two factors were independently associated with PFS (p=0.028 and 0.0062, respectively; Table III). PFS curves among patients with both

Table III. Univariate and multivariate analysis of progression-free survival.

	Univariate analysis	Multivariate analysis		
Variables	P-value	HR	95% CI	P-value
Gender (male/female)	0.76	N.I.		
Age (<70/≥70 years)	0.14	N.I		
Location (upper/middle, lower)	0.3	N.I		
cT (T1-2/T3)	0.031	2.16	1.08-4.29	0.028
cN (N0-1/M1 LYM)	0.57	N.I.		
Early response status (early responder/early non-responder)	0.032	2.28	1.26-4.12	0.0062

HR, hazard ratio; CI, confidence interval; N.I., not included.

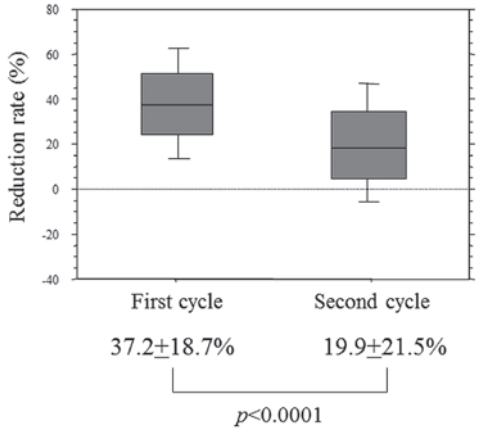

Figure 1. Reduction rate of the primary tumor. The reduction rate after the second cycle was significantly worse compared to that after the first cycle (p<0.0001).

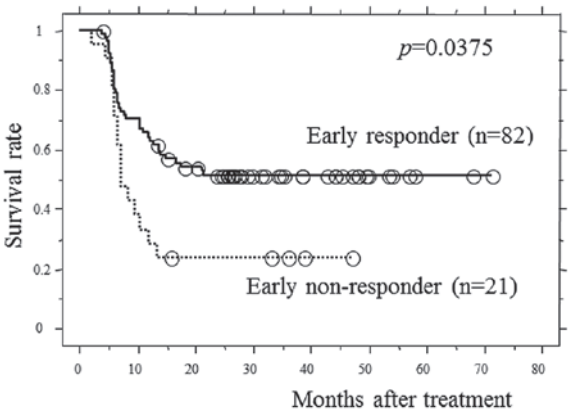

Figure 2. Progression-free survival curves according to early response status. Early responders had significantly improved progression-free survival compared to early non-responders (p=0.0375).

unfavorable factors (group A; T3 and early non-responders), those with no unfavorable factors (group C; T1-2 and early responders) and the remaining patients (group B; others) were examined. Group A had a significantly worse PFS when compared to groups B and C (p=0.0079 and 0.0004, respectively; Fig. 3) .

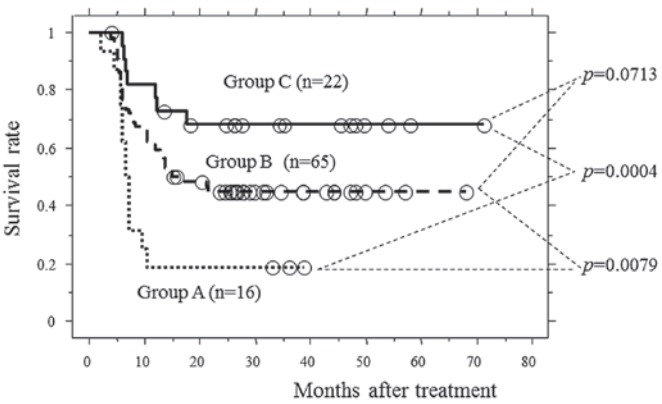

Figure 3. Progression-free survival curves according to clinical T stage and early response status. Group A had a significantly worse progression-free survival compared to groups B and C (p=0.0079 and 0.0004, respectively). Group A, patients with both unfavorable factors (T3 tumor and early non-responder status); Group B, others; Group C, patients with no unfavorable factors (T1-2 tumor and early responder status).

Significance of the second cycle of chemotherapy in group A patients. Twenty-five patients discontinued NACT after the first cycle due to ineffectiveness and underwent esophagectomy. Among these patients, 17 had clinical T3 tumors and exhibited <20% decrease in the size of the primary tumor following the first cycle of NACT (group D). To investigate the significance of the second cycle of chemotherapy in group A patients, we compared PFS between group A and group D patients. No significant differences in the baseline clinical factors and the reduction rate after the first cycle of chemotherapy between the 2 groups were observed (Table IV). No significant difference were identified in PFS between the 2 groups (Fig. 4).

Discussion

Multiple cycles of cisplatin-based chemotherapy is a standard protocol for NACT for advanced esophageal cancer. In order to avoid the repetition of ineffective therapy in non-responders, it is important to establish criteria for discontinuing NACT after the first cycle. In early non-responders (patients with <20% decrease in the size of the primary tumor after the first cycle of chemotherapy), the reduction rate after the second

Table IV. Clinical characteristics of group A and group D patients.

Variables	Group A[b] (n=16)	Group D[c] (n=17)	P-value
Gender			
Male	16	14	0.24
Female	0	3	
Age (years)			
<70	14	14	0.99
≥70	2	3	
Location			
Upper	1	1	0.27
Middle	9	5	
Lower	6	11	
cT[a]			
T3	16	17	
cN[a]			
N0-1	10	14	0.81
M1 LYM	6	3	
Reduction rate of the first cycle of NACT	11.2±7.4%	5.6±13.4%	0.16

[a]cT and cN are as defined by the 6th edition of the TNM classification. [b]Group A: Patients with both unfavorable factors (T3 tumor and early non-responder status) received 2 cycles of NACT. [c]Group D: Patients with both unfavorable factors (T3 tumor and early non-responder status) received 1 cycle of NACT. NACT, neoadjuvant chemotherapy.

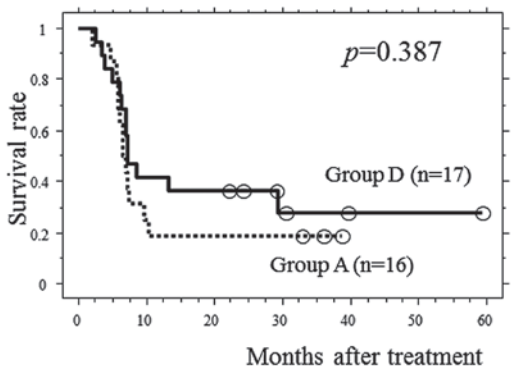

Figure 4. Progression-free survival curves of groups A and D. Group A, patients with both unfavorable factors (T3 tumor and early non-responder status) who received 2 cycles of neoadjuvant chemotherapy (NACT). Group D, patients with both unfavorable factors (T3 tumor and early non-responder status) who received 1 cycle of NACT. No significant difference was observed between the 2 groups.

cycle of chemotherapy, PFS and pathological factors (pathological T stage, pathological response of the primary tumor and number of metastatic lymph nodes) were significantly worse. Therefore, evaluation of early response with CT may be a useful method for identifying patients likely to have unfavorable outcomes after a number of courses of NACT. Among the clinical variables available prior to administration of the second cycle of NACT, clinical T3 stage and early non-responder status were independent unfavorable prognostic factors, and patients with the two factors exhibited significantly poorer PFS. Moreover, there was no significant difference between the prognosis of patients who had both unfavorable factors and received 1 or 2 cycles of NACT. Therefore, in patients with both unfavorable prognostic factors, the second cycle of NACT should be avoided, and patients should undergo salvage therapies, such as alternative chemotherapy regimens, chemoradiotherapy, or immediate surgery. Such an individualized approach may improve prognosis by reducing the length of time during which a patient receives ineffective therapy.

Previous studies have demonstrated that metabolic response as measured by positron emission tomography (PET) may help differentiate between responding and non-responding esophageal cancers early in the course of therapy (13-15). Weber *et al* (15) reported that changes in tumor metabolic activity after 14 days of NACT, as assessed using PET, were significantly correlated with histopathological response and survival rates. However, CT is more prevalent and PET is associated with issues regarding the complexity of the technology and the absence of standardization for metabolic imaging.

Among baseline factors, clinical T stage was significantly correlated with prognosis, as opposed to clinical N stage. Clinical T stage was significantly correlated with pathological T stage (p=0.0001). There was no correlation between clinical N stage and the number of metastatic lymph nodes. This may be partly attributed to the fact that we administered NACT mainly to clinically node-positive esophageal cancer patients. The rate of early response was significantly higher in females compared to males. Overall response (after the second cycle of NACT) was also significantly higher in females (p=0.0011, data not shown). The response to chemotherapeutic agents may be partly determined by drug concentration in the tumor environment (16,17). Investigators have previously suggested that gender-specific pharmacokinetics exist for certain

chemotherapeutic agents. Milano *et al* (18) reported that the capacity to clear 5-FU is lower in women than in men. Dobbs *et al* (19) demonstrated that, among patients with normal liver function, men exhibit a higher rate of doxorubicin clearance compared to women. Higher response to chemotherapy in females observed in this study may partly be due to the higher blood concentrations of chemotherapeutic agents.

The reduction rate after the second cycle was significantly worse compared to that after the first cycle. This was consistent with a previous study (20). It is likely that tumors are heterogeneous and the first cycle eliminates only the sensitive tumor cells, sparing resistant tumor cells (21). Another reason is that the first cycle may eliminate tumor cells located around the tumor vessels with a high drug concentration and the second cycle may kill tumors distant from the tumor vessel with a low drug concentration. The efficacy of chemotherapy may deteriorate as the number of cycles increases. When administering multiple cycles of NACT, physicians should evaluate chemotherapeutic response following completion of each cycle of chemotherapy.

Early non-responders were defined as the patients with <20% decrease in the size of the primary tumor after the first cycle of chemotherapy. When the cut-off value was set at 30%, the reduction rate after the second cycle chemotherapy, PFS, pathological T stage and pathological response were significantly worse in early non-responders, although there was no significant difference in the number of metastatic lymph nodes between the 2 groups. When the cut-off value was set at 10%, there was no significant difference in PFS between the 2 groups. The relatively low threshold of 20% may be appropriate, since it ensures that all patients who potentially benefit from NACT receive further treatment.

In conclusion, this study has demonstrated that the reduction rate of the primary tumor as evaluated by CT after the first cycle of NACT may aid physicians in determining whether to administer the second cycle. In patients with T3 tumors and <20% decrease in the size of the primary tumor after the first cycle of chemotherapy, NACT should be discontinued after the first cycle.

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